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**The Ireland-Claisen rearrangement of 3-alkoxypropenol amino esters as an entry to sphingolipid amino acid natural products**

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# **THE IRELAND-CLAISEN REARRANGEMENT OF 3- ALKOXYPROPENOL AMINO ESTERS AS AN ENTRY TO SPHINGOLIPID AMINO ACID NATURAL PRODUCTS**

Nathan William George Fairhurst

A thesis submitted for the degree of Doctor of Philosophy

University of Bath

Department of Chemistry

July 2012

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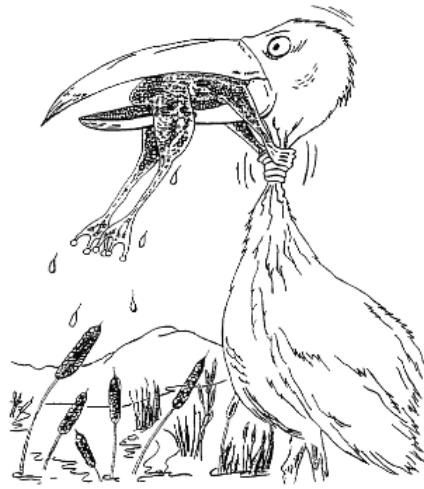
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**ABSTRACT**

The Ireland-Claisen rearrangement is a powerful synthetic tool which allows predictable diastereocontrol and chirality transfer in the synthesis of  $\gamma,\delta$ -unsaturated carboxylic acids. Previous work within the Carbery group has developed a novel protocol for the synthesis of  $\beta$ -alkoxy- and aryloxy- $\alpha$ -amino acids.

Chapter 2 covers the initial volume of work on developing this methodology further to allow the synthesis of sterically congested  $\alpha$ -quaternary carbon centres in  $\beta$ -alkoxy- and aryloxy- $\alpha$ -amino acids. Individual substrate optimisation allowed improvement of both the yields and diastereoselectivity of this rearrangement, along with the isolation of a key degradation product. A series of heteroproline-based rearrangements laid the groundwork for remote chirality transfer within this Ireland-Claisen rearrangement.

The principle of self-regeneration of stereocentres is applied in an Ireland-Claisen context in Chapter 3. Showing exceptional levels of remote stereocontrol the rearrangement is shown to be general, offering almost exclusively diastereoselectivities of  $>99:1$ . Allylic enol ether amino esters saw yields of 47 – 83% and provided functional handles allowing for further synthetic manipulations. Carbon substituted allyl amino esters allowed facile access into  $\beta$ -hydroxy- $\alpha$ -amino acid derivatives of proteinogenic amino acids leucine and isoleucine (amongst others) with excellent selectivity.

The synthesis of both enantiomers of mycestericin G in Chapter 4 highlights the synthetic utility of this methodology, in addition to allowing a revision of absolute configuration of this natural product. The synthesis of a mycestericin G analogue, derived from threonine, is also presented.

Finally, Chapter 5 exploits these rearrangement products as chiral diene ligands in rhodium-catalysed conjugate addition reactions. Both ligand and reaction condition optimisation led to a range of aryl boronic acids used in the 1,4-addition to 2-cyclohexenone with yields of 24 – 100% and enantioselectivities of 74 – 93% observed.

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**ABBREVIATIONS**

AAA	asymmetric allylic alkylation
acac	acetylacetonate
Ac	acetyl
AIBN	azo-bis-isobutyronitrile
Ar	aryl
Bn	benzyl
Boc	di- <i>tert</i> -butyl dicarbonate
<sup>i</sup> Bu	<i>iso</i> -butyl
<sup>n</sup> Bu	<i>n</i> -butyl
<sup>s</sup> Bu	<i>sec</i> -butyl
<sup>t</sup> Bu	<i>tert</i> -butyl
Bz	benzoyl
ca.	circa
cat.	catalytic
Cbz	carboxybenzyl
cod	cyclooctadiene
CoA	coenzyme A
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
DCE	dichloroethene
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
(+)-DIPT	(+)-diisopropyl L-tartrate
(-)-DIPT	(-)-diisopropyl D-tartrate
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMPU	<i>N,N'</i> -dimethylpropyleneurea

DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
DS	Dean Stark
DTA	D-threonine aldolase
EDCi	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride
ee	enantiomeric excess
<i>ent</i> -	enantiomer
<i>epi</i> -	epimer
eq	equivalents
Et	ethyl
EtOAc	ethyl acetate
HIV	human immunodeficiency virus
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
hrs	hours
Hz	hertz
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
LiICA	lithium isopropylcyclohexylamide
LTA	L-threonine aldolase
<i>m</i> -	<i>meta</i>
<i>m</i> -CPBA	<i>meta</i> -chloroperoxybenzoic acid
Me	methyl
MIC	minimum inhibitory concentration
min	minute
MOM	methoxymethyl ether
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
Ms	methanesulphonyl
MTBE	methyl <i>tert</i> -butyl ether
NaMDS	sodium bis(trimethylsilyl)amide
Naphth	naphthalene
nbd	norbornadiene

NBS	<i>N</i> -bromo succinimide
NCS	<i>N</i> -chloro succinimide
NEt <sub>3</sub>	triethylamine
NMO	<i>N</i> -methylmorpholine <i>N</i> -oxide
NMP	<i>N</i> -methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Nu	nucleophile
Nva	norvaline
<i>o</i> -	<i>ortho</i>
<i>p</i> -	<i>para</i>
PLP	pyridoxal phosphate
PMB	<i>para</i> -methoxybenzyl
PMP	<i>para</i> -methoxyphenyl
Ph	phenyl
Phth	phthaloyl
ppm	parts per million
PPTS	pyridinium <i>p</i> -toluenesulphonate
<sup>i</sup> Pr	<i>iso</i> -propyl
<sup>n</sup> Pr	<i>n</i> -propyl
Py	pyridine
RT	room temperature
SAR	structure-activity relationship
SHMT	serine hydroxymethyltransferase
SPT	serine palmitoyltransferase
SRS	self-regeneration of stereocentres
TBAF	tetrabutylammonium fluoride
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
temp	temperature
Tf	trifluoromethylsulphonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography

TMS	trimethylsilyl
Tol.	toluene
Ts	<i>para</i> -toluenesulfonyl
Val	valine
VRE	vancomycin-resistant enterococci
VT	variable temperature
XRD	X-ray diffraction

## 1. INTRODUCTION

### 1.1 $\beta$ -Hydroxy- $\alpha$ -Amino Acids

Compounds that contain both amine and carboxylic acid functional groups are classed as amino acids. They can vary in the number of carbon linkers between the functional groups, and are typically identified by this linkage;  $\alpha$ -amino acids feature the amine and carboxylic acid bonded to the same  $\alpha$ -carbon, whilst  $\beta$ -amino acids feature a chain of two carbons separating these groups (Figure 1).

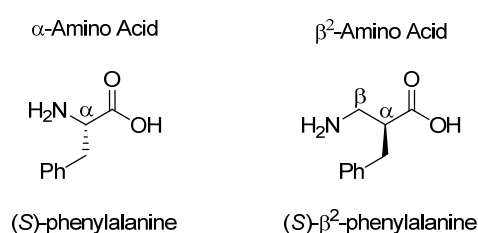


Figure 1 -  $\alpha$ - and  $\beta$ -Amino acids

There are twenty natural proteinogenic amino acids that are found within proteins that are coded for in the genetic code.<sup>1</sup> Proteinogenic means ‘protein-building’, and it is these twenty amino acids that make up the proteins and peptides that are vital for life.<sup>1-2</sup> Two of these proteinogenic amino acids (threonine and serine, Figure 2) can be further classified as  $\beta$ -hydroxy- $\alpha$ -amino acids.<sup>3</sup>

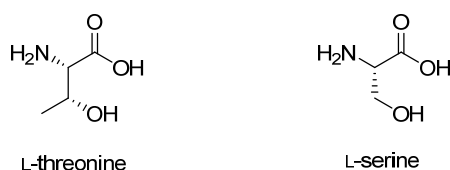


Figure 2 - L-Threonine and L-serine

Threonine is one of eight essential amino acids. These eight amino acids are so called because their synthesis can't occur within the body, but must be obtained through food or other sources.<sup>4-5</sup> Serine meanwhile is considered to be a non-essential amino acid, as, in healthy adults, it can be synthesised in the body *via* a condensation reaction between glycine and activated formaldehyde. However, this is not the case for patients with poor

kidney function, where synthesis may not cover serine requirements, and hence supplements are needed.<sup>4</sup>

Natural products in their own right,  $\beta$ -hydroxy- $\alpha$ -amino acids are also found as components of more complex compounds, a significant number of which have noteworthy biological activity.<sup>6-7</sup> For example, vancomycin and lysobactin demonstrate considerable antibiotic activity, while cyclosporine acts as an immunosuppressant commonly used clinically to suppress the rejection of transplanted human organs.<sup>8-10</sup>

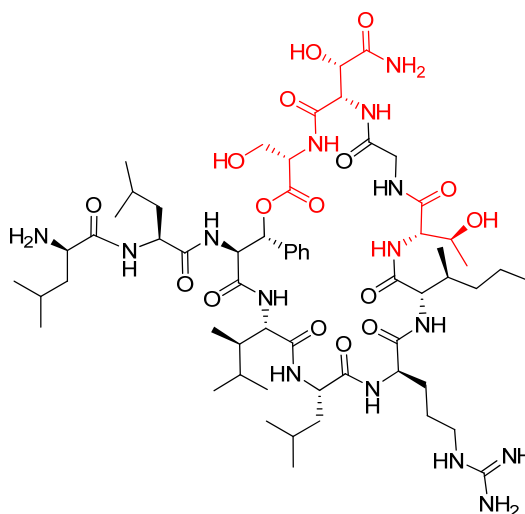


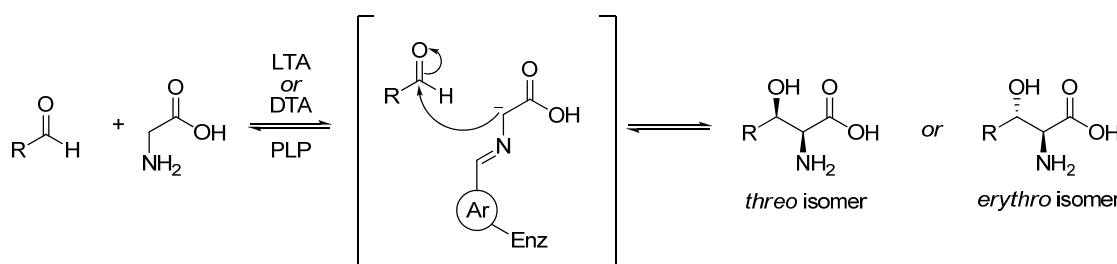
Figure 3 - Lysobactin<sup>11</sup>

Of recent interest is lysobactin (Figure 3), a cyclic depsipeptide which features several  $\beta$ -hydroxy- $\alpha$ -amino acid units. First isolated from a species of *Lysobacter* (ATCC53042), lysobactin shows strong antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA).<sup>12-13</sup> Although the mode of action for lysobactin is not precisely known, data suggests that it may be due to inhibition of transglycosylation and its preceding steps of cell wall peptidoglycan synthesis. This mode of action is different to that of vancomycin, the usual last resort antibiotic. Indeed, the minimum inhibitory concentrations (MICs) ranged between 0.39 to 0.78  $\mu\text{g/mL}$  for MRSA and vancomycin-resistant enterococci (VRE), greater than 50-fold lower than those reported for vancomycin itself.<sup>14</sup>

### 1.1.1 Synthesis of $\beta$ -Hydroxy- $\alpha$ -Amino Acids

Due to their biological importance much effort has been directed towards the synthesis of  $\beta$ -hydroxy- $\alpha$ -amino acids. As a result there are many strategies for their synthesis, including Sharpless asymmetric epoxidations<sup>15-17</sup>, Strecker synthesis<sup>18</sup>, aza-Claisen rearrangements<sup>19</sup>, Wittig rearrangements<sup>8</sup>, and a number of aldol reactions<sup>20-24</sup>, including some catalysed enzymatically.<sup>6-7, 25</sup>

The aldol reaction has received much attention as an efficient route to asymmetric  $\beta$ -hydroxy- $\alpha$ -amino acids. One of the simplest strategies involves the use of threonine aldolases and serine hydroxymethyl transferases in the enzyme-catalysed asymmetric aldol reaction. Wong *et al.* were able to exploit L-threonine aldolase (LTA) and D-threonine aldolase (DTA) with the use of pyridoxal phosphate (PLP) coenzyme to activate glycine to react with a range of aldehydes (Scheme 1).<sup>6</sup>



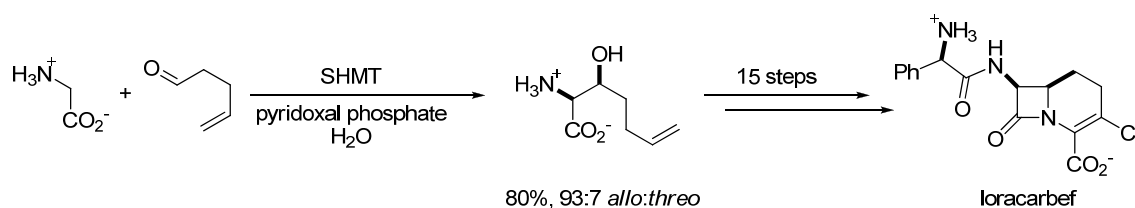
**Scheme 1 - Enzymatic synthesis of  $\beta$ -hydroxy- $\alpha$ -amino acids based on D- and L-threonine aldolases**

The kinetically controlled products from LTA were *erythro*- $\beta$ -hydroxy- $\alpha$ -L-amino acids from aliphatic aldehydes, and the *threo* isomer with aromatic aldehydes, whilst DTA formed *threo*- $\beta$ -hydroxy- $\alpha$ -D-amino acids with both aliphatic and aromatic aldehydes. A series of studies with respect to the enzyme's kinetics, specificity and stability, among others, found that the enzymes were stable with little loss of activity over a period of one week. Overall it was demonstrated that the enzymes accept an extensive range of aldehydes as acceptors, allowing a route to either L- or D- $\alpha$ -amino acids, albeit with an epimeric mixture at the  $\beta$ -carbinol centre.

A group from Eli Lilly demonstrated the enantioselective synthesis of the oral carbacephalosporin antibiotic loracarbef (Lorabid<sup>®</sup>) from L-*erythro*-2-amino-3-hydroxy-

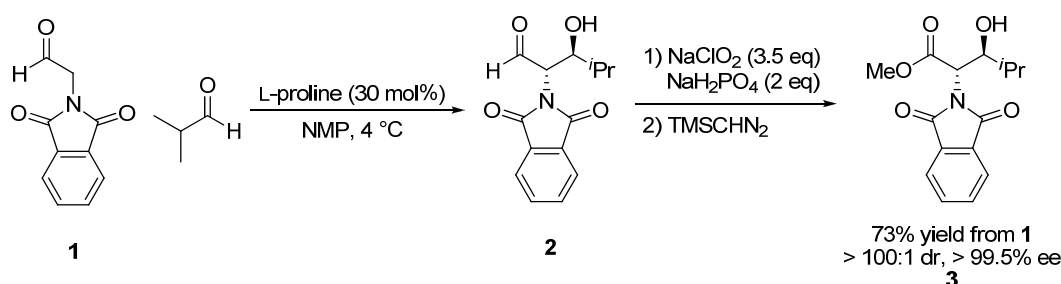


6-heptenoic acid, synthesised by the serine hydroxymethyltransferase (SHMT) catalyzed condensation between glycine and 4-pentaldehyde (Scheme 2).<sup>25</sup>



**Scheme 2 - SHMT catalyzed synthesis of  $\beta$ -hydroxy- $\alpha$ -amino acids in the total synthesis of antibiotic loracarbef**

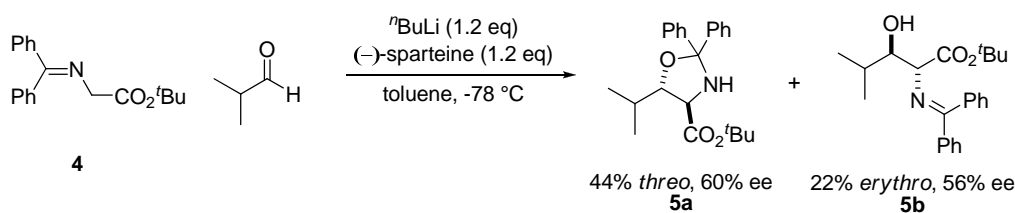
The success of enzyme-catalyzed aldol reactions has prompted many groups to examine other forms of catalytic aldol reactions as routes into  $\beta$ -hydroxy- $\alpha$ -amino acids. One such group is that of Barbas III *et al.*, where efficient asymmetric aldol reaction of a glycine aldehyde derivative utilising organocatalysis using L-proline has been developed (Scheme 3).<sup>22</sup>



**Scheme 3 - Direct organocatalytic synthesis of enantiometrically enriched  $\beta$ -hydroxy- $\alpha$ -amino acids**

Good yields, high diastereoselectivity and excellent enantioselectivity were seen in this reaction. The use of phthalimidoacetaldehyde **1** was key for the reaction, as it allowed selective reactivity of the enamine intermediate. For analytical purposes the methyl ester was synthesised using trimethylsilyl diazomethane immediately after the oxidation of the aldehyde **2** with sodium chlorite. However, the free amino acid was able to be synthesised by deprotection of the phthalimide with hydrazine as opposed to methylation.

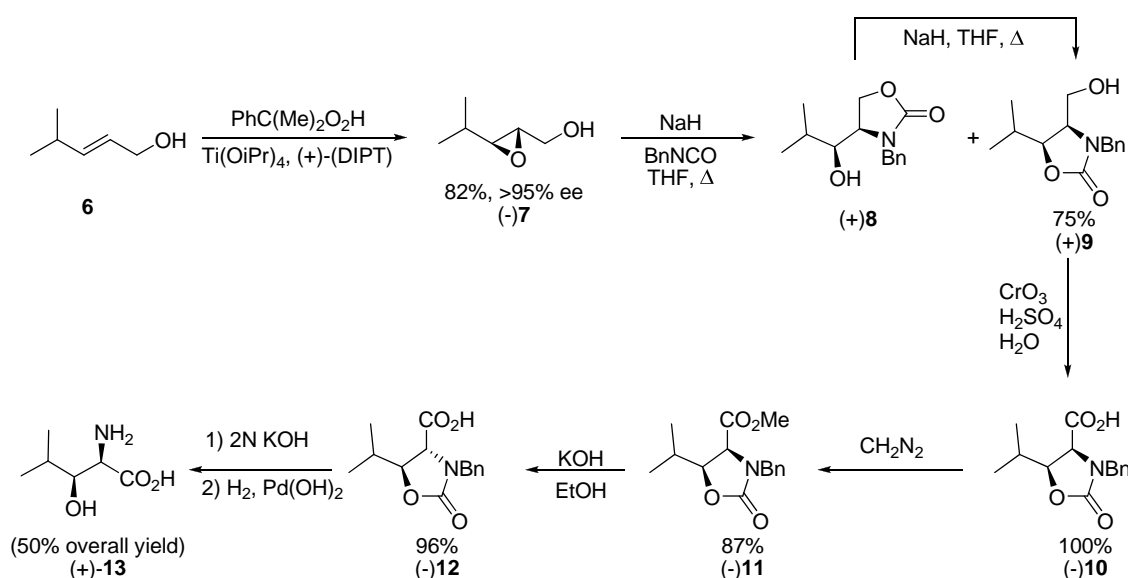
Another highly explored area within aldol based chemistry is using glycinate Schiff bases as donors.



**Scheme 4 - Synthesis of  $\beta$ -hydroxy- $\alpha$ -amino acids by  $(-)$ -sparteine-mediated aldol addition**

Demonstrated by Molinski *et al.*, addition of isobutyraldehyde to the lithium enolate of **4** produced a mixture of *threo*-oxazolidine **5a** and *erythro*-imine **5b** (Scheme 4).<sup>23</sup> After separation by chromatography, analysis by chiral HPLC showed enantioselectivities of 60% and 56% respectively. These were readily converted to the corresponding  $\beta$ -hydroxyleucines by hydrolysis-hydrogenolysis. These optically active amino acids were required for the configurational analysis of lobocyclamide B, a novel antifungal cyclododecapeptide, isolated from *Lyngbya confervoides* in the Bahamas.

In 1993, Satoshi Omura presented an efficient asymmetric synthesis of all four stereoisomers of 3-hydroxyleucine, utilising a Sharpless asymmetric epoxidation and benzyl isocyanate-induced epoxide opening as the key steps (Scheme 5).<sup>17</sup>

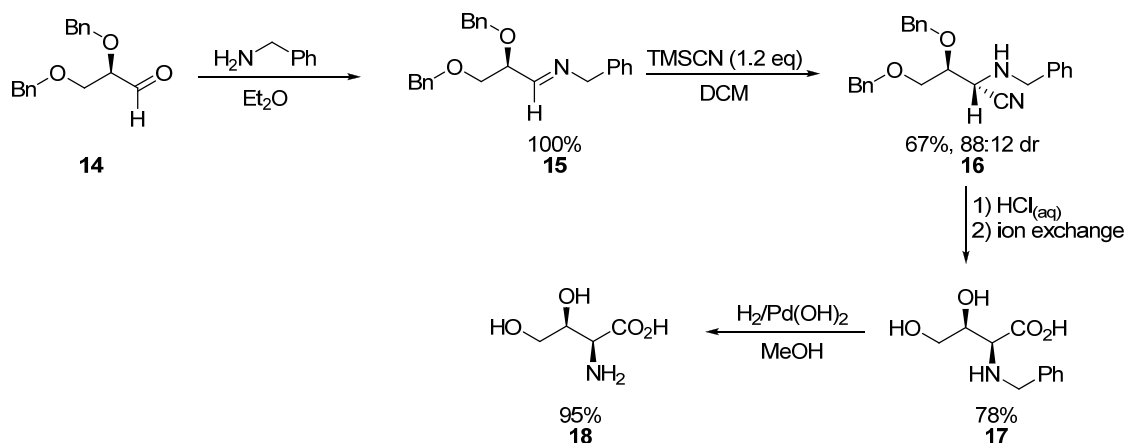


**Scheme 5 - Synthesis of (2*R*,3*S*)-3-hydroxyleucine (+)-13**

The synthetic strategy started with the Sharpless asymmetric epoxidation of **6**, affording epoxide **7** in 82% yield and greater than 95% ee. A mixture of regioisomeric oxazolidinones were formed after treatment with benzyl isocyanate and sodium hydride.

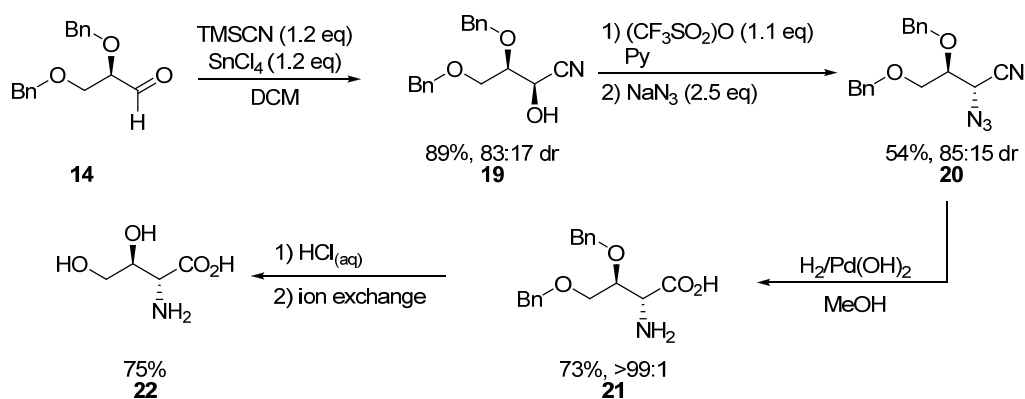
After exposure to additional sodium hydride, heterocycle **9** was formed as a single product, and subsequent Jones oxidation yielded carboxylic acid **10**. The (2*S*,3*S*)-isomer was synthesised by carbamate deprotection and hydrogenolysis of **10**. Synthesis of the (2*R*,3*S*)-isomer however required two more steps; diazomethane esterification, followed by epimerization and saponification before finishing the synthesis with carbamate deprotection and hydrogenolysis to afford (2*R*,3*S*)-3-hydroxyleucine in 50% overall yield. The opposite enantiomers were synthesised through the same methodology, simply replacing (+)-DIPT with (–)-DIPT in the epoxidation of **6**.

The Strecker reaction was employed by Cativiela *et al.* in their synthesis of (2*S*,3*S*)- and (2*R*,3*S*)-2-amino-3,4-dihydroxybutyric acid (**18** and **22** respectively), however they required the use of two alternate routes to obtain the two diastereomers (Scheme 6 and Scheme 7 respectively).<sup>18</sup>



Scheme 6 - Synthesis of (2*S*,3*S*)-2-amino-3,4-dihydroxybutyric acid **18**

Schiff base **15** was prepared by condensation between aldehyde **14** and benzylamine, preceding a Strecker reaction to afford **16** in an 88:12 diastereomeric ratio. The diastereomers were readily separable by column chromatography allowing the synthesis to continue. Nitrile hydrolysis with simultaneous *O*-benzyl deprotection with hydrochloric acid afforded the *N*-benzyl amino acid after purification by ion-exchange chromatography. Hydrogenolysis in the presence of Pearlman's catalyst yielded the required (2*S*,3*S*)-2-amino-3,4-dihydroxybutyric acid **18**, with the absolute configuration and optical purity being confirmed by literature comparison (Scheme 6).

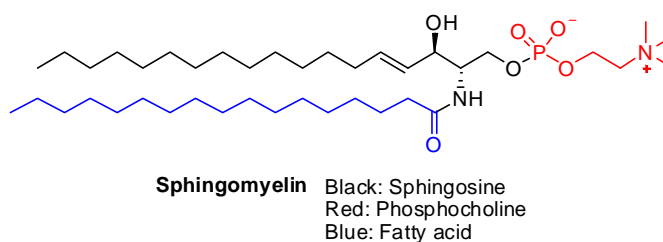


**Scheme 7 - Synthesis of (2*R*,3*S*)-2-amino-3,4-dihydroxybutyric acid 22**

Synthesis of the (2*R*,3*S*)- isomer was achieved by diastereoselective cyanide addition to **14** utilising tin tetrachloride as a Lewis acid. Treatment with trifluoromethanesulfonic anhydride, sodium azide and then hydrogenolysis with Pd/C afforded the amino nitrile **21**. Following separation of diastereomers by flash chromatography, acid hydrolysis and ion exchange chromatography afforded the (2*R*,3*S*)-2-amino-3,4-dihydroxybutyric acid **22** with a specific rotation matching that in the literature (Scheme 7).

## 1.2 Sphingosine and Sphingosine-related Metabolites

The term sphingolipid was proposed by Herb Carter in 1947 to describe a complex range of lipids in which fatty acids have a simple amide bond to a sphingoid base backbone.<sup>26-27</sup> This sphingoid base can be further phosphorylated, acylated, glycosylated or bridged to various headgroups to create the thousands of sphingolipids that have been elucidated to this date. The most common long-chain base is sphingosine, first discovered by Johann Thudichum in 1884 on the hydrolysis of the three lipids sphigomyelin, cerebroside, and cerebrosulfatide.<sup>28</sup>

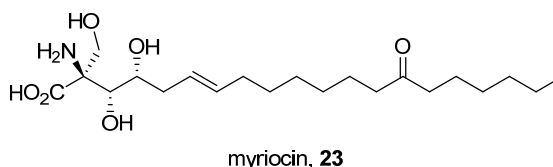


**Figure 4 - Sphingomyelin**

Sphingolipids are important components of all mammalian membranes, of which sphingomyelin is the most abundant (Figure 4). The basic structural units of sphingolipids in the human cell typically start from dihydrosphingosine (more commonly known as sphinganine); which is synthesised in nature from serine and palmitoyl-CoA by serine palmitoyltransferase (SPT). From here it can follow a myriad of pathways until the desired sphingolipid is formed.<sup>29</sup> Not only do sphingolipids play a structural role, but they are also important in cellular regulation and signal transmission.<sup>29-31</sup> It is now known that sphingolipids are involved in almost every type of disease, from being the binding target for bacteria<sup>32</sup>, to causing the toxicity of fumonisins<sup>33-34</sup> (a common food contaminant worldwide) through disruption of *de novo* sphingolipid biosynthesis. They are known to be used by cells to coordinate cell division and survival in cases of cancer – they even showed chemotherapeutic potential in experimental human clinical trials.<sup>35-36</sup> The list continues with implications in Alzheimer's disease<sup>37-39</sup>, and also acting as immunosuppressants.<sup>40</sup> As such, sphingolipid-based therapeutics is an ever increasing area of interest to researchers who are trying to steer a course through the complex mechanisms – and occasional contradictory findings – presented from such a large number of structurally and metabolically interrelated bioactive species.<sup>29</sup>

### 1.2.1 Isolation and Biology of Sphingosine Analogues

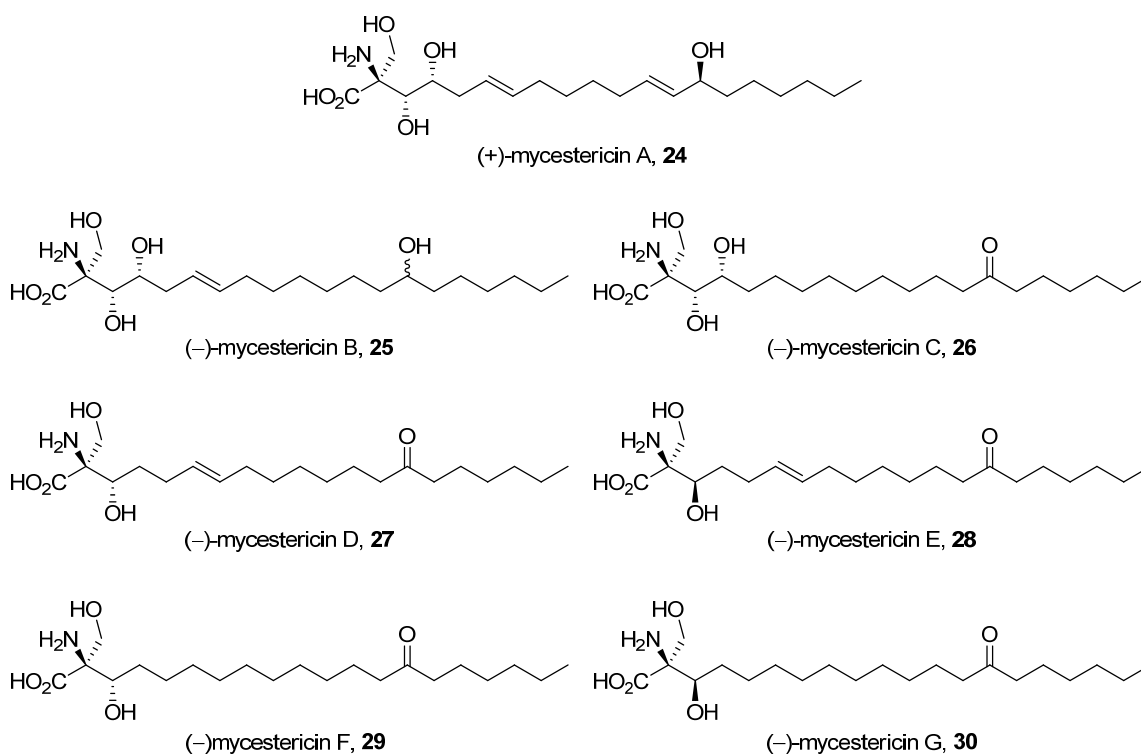
Since sphingosine was discovered by Thudichum, a host of related compounds have been isolated. In the early 1970s one such metabolite was discovered almost simultaneously by two research groups. In 1971, Dieter Kluepfel isolated the novel antifungal compound, myriocin **23** (Figure 5), from *Myriococcum albomyces*, a thermophilic fungus.<sup>41-42</sup> They demonstrated that myriocin showed no significant antimicrobial activity, but that it did however, show strong antifungal activity *in vitro*. Meanwhile, in 1972, Fabrizio Aragozzini reported the isolation of thermozymocidin, a metabolite of the thermophilic mould *Mycelia sterilia*.<sup>43</sup> The structure and properties of thermozymocidin were identical to **23**. More recently, the culture broths of *Melanconis flavovirens* and *Isaria sinclairii* have also been found to contain **23**.<sup>44-45</sup> This family of fungi have been used in traditional Chinese medicine as a drug for 'eternal youth'.<sup>46</sup>



**Figure 5 - Potent immunosuppressant, myriocin**

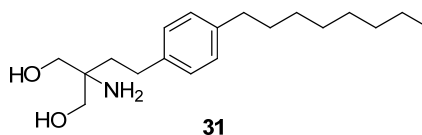
It was however, Fujita *et al.* who, on isolating **23**, realised its potential as a potent immunosuppressive agent.<sup>45</sup> They found that it suppressed the proliferation of lymphocytes in mouse allergenic mixed lymphocyte reaction, and was 10- to 100-fold more potent than cyclosporine A; an immunosuppressive drug approved for use in the 1980s.<sup>47-48</sup>

On further analysis of the culture broth of *Mycelia sterilia*, Fujita *et al.* were also able to isolate and elucidate the structures of a new class of 7 metabolites which they termed the mycestericins.<sup>49-50</sup> Mycestericin A **24**, B **25**, and C **26** were reported to be congruent to **23** with respect to their polar head group, featuring the same hydroxy group substitution and stereochemistry. Mycestericins D **27** through to G **30** lack the secondary  $\gamma$ -hydroxy group, and form two pairs of diastereomers.



**Figure 6 - Mycestericins A-G**

Structure activity relationships (SAR) between myriocin **23** and the mycestericins (**24-30**) using mouse allogenic mixed lymphocyte reaction *in vitro* were built to evaluate the influence of the structural features of these immunosuppressants.<sup>51</sup> It is from similar SARs that allowed the derivative fingolimod **31** to be identified (Figure 7).

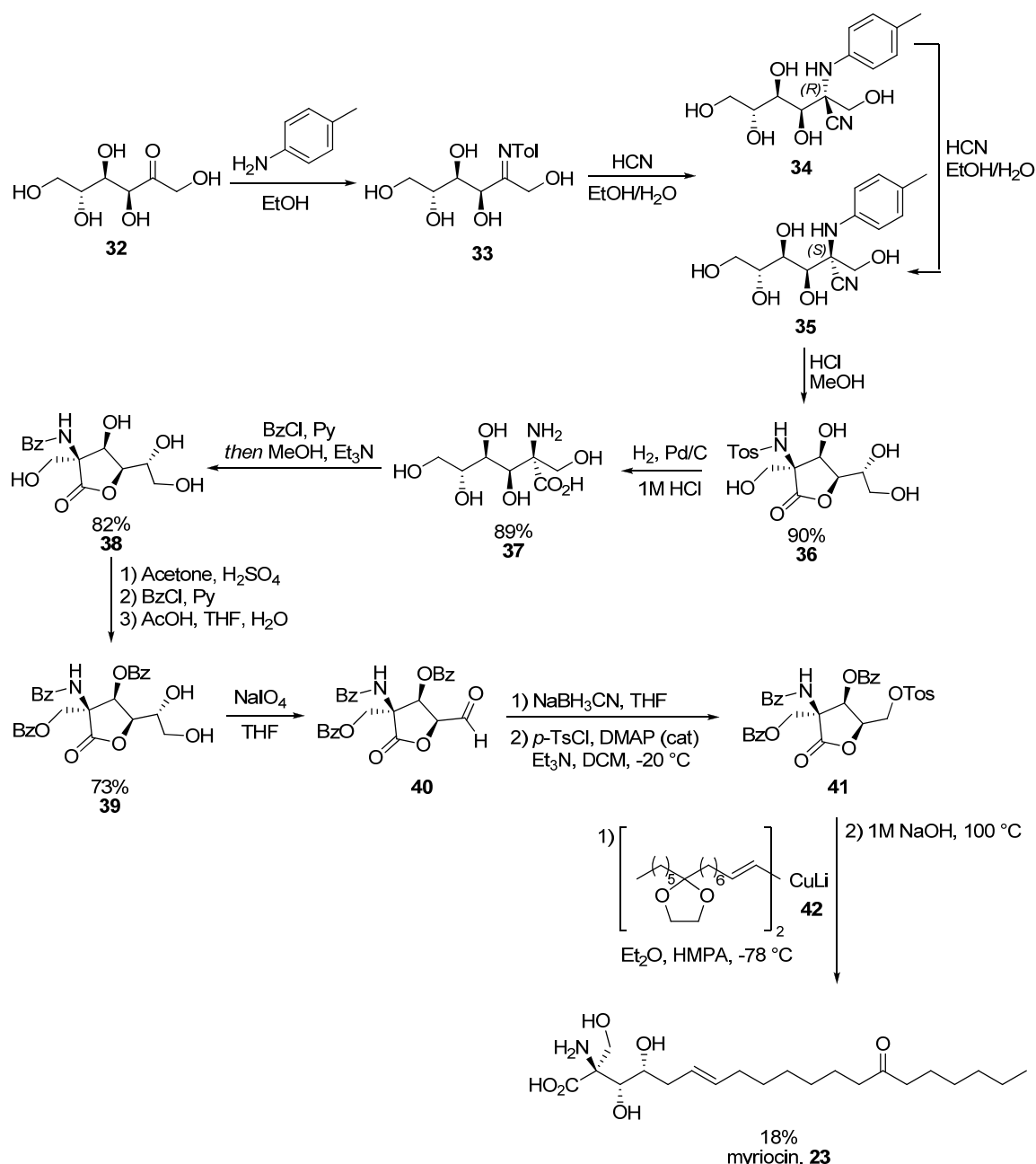


**Figure 7 - Fingolimod**

Originally in phase III clinical trials for use in kidney transplants, fingolimod was found to have no advantages over the existing standard of care.<sup>52-53</sup> However, in two phase III trials, it was seen to reduce the rate of relapses in relapse-remitting multiple sclerosis.<sup>54</sup> Now marketed by Novartis as Gilenya<sup>™</sup>, it is advertised as the “first once-daily pill for relapsing forms of multiple sclerosis”.<sup>55</sup> Whilst its mode of action in humans is not fully understood, it is believed to sequester lymphocytes in the lymph nodes, reducing the number that can move to the central nervous system which cause the auto-immune responses seen in multiple sclerosis.<sup>56</sup>

### 1.2.2 Synthesis of Sphingosine Analogues

Soon after the discovery of myriocin, two groups accomplished the synthesis of chiral  $\gamma$ -lactones derived from myriocin.<sup>57-59</sup> However, it wasn't until 1982 when Scolastico *et al.* published the first total synthesis of myriocin.<sup>60-61</sup> Completed in 15 linear steps D-fructose **32** was utilised as the chiral synthon (Scheme 8). The key aim was to achieve the synthesis of 2-amino-2-deoxy-2-hydroxymethyl-D-mannonic acid **37**, from which all the key stereocentres would be installed. Hydrocyanation of fructosyl *p*-tolylimine **33** afforded two diastereomers, in a 7:2 mixture. Unfortunately the desired (2*S*)-epimer **35** was the minor component in this mixture. By subjecting (2*R*)-epimer **34** to an excess of hydrogen cyanide in ethanol-water, partial conversion to the desired diastereomer was achieved.



Scheme 8 – First total synthesis of myriocin

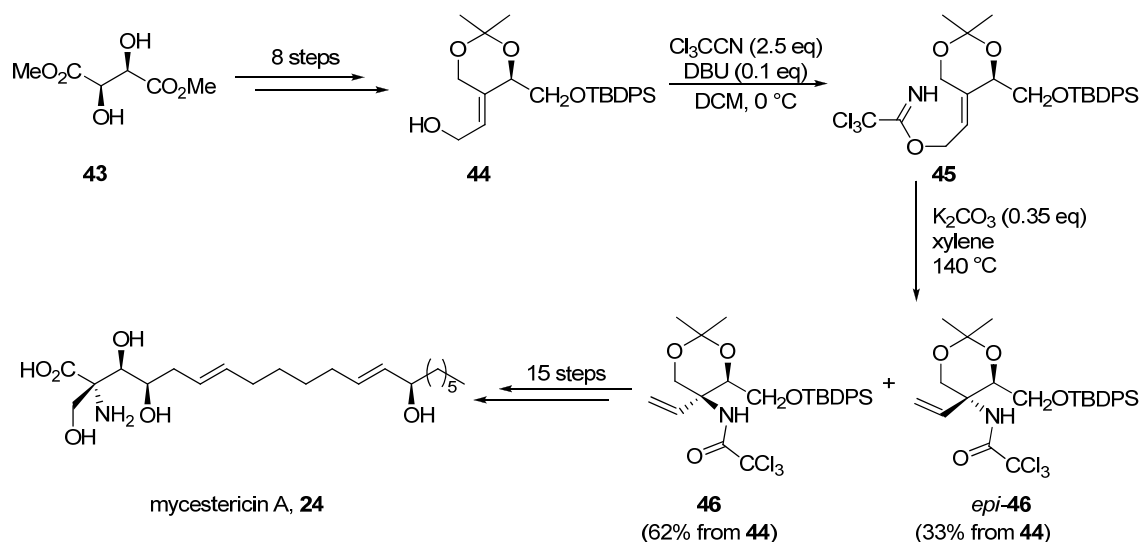
Hydrolysis with concentrated hydrochloric acid, before removal of the *N*-tolyl protecting group by hydrogenolysis afforded key amino acid **37**. Schotten-Baumann conditions gave a poor yield of **38**, whereas treatment with excess benzoyl chloride in pyridine, followed by methanolysis of the benzoyl ester gave the lactone **38** in 60% yield. Initial attempts to perform a sodium periodate oxidation gave rise to an undesired hemiacetal dimer. To avoid this dimer, **38** was treated with acetone and catalytic sulphuric acid, followed by esterification with benzoyl chloride, before final hydrolysis of the isopropylidene acetal afforded the diol **39**. Sodium periodate oxidation, subsequent sodium cyanoborohydride reduction and tosylation yielded the tosyl lactone



**41** necessary for coupling to the lithium divinylcuprate **42**. This cuprate was synthesised in 9 steps from 1-morpholinocyclohexene and, with the use of HMPA as a co-solvent, successfully coupled with **41** to afford the protected anhydromyriocin in a relatively low yield of 28%. Final hydrolysis of the benzoyl protecting groups provided synthetic (+)-myriocin **23**, indistinguishable from the naturally obtained compound.

Since this initial total synthesis there have been many other attempts to synthesis both (+)-myriocin **23**, and its enantiomer (–)-myriocin.<sup>62</sup> Yoshikawa and co-workers also looked to utilise a natural carbohydrate as an optically pure starting material, opting to start with 2-deoxy-D-glucose, and featuring a modified Darzens reaction as one of their key steps.<sup>63-64</sup> Highly diastereoselective aldol reactions were employed by both Nagao and Lee, with the former using D-valine to synthesise a chiral bislactim ether, and the latter using an oxazoline framework as the basis of their approach.<sup>65-66</sup> Many approaches have focused on epoxide opening, with Hatakeyama *et al.* using Katsuki-Sharpless catalytic asymmetric epoxidation to synthesise an enantiomerically pure epoxide, opened using Red-Al®.<sup>67</sup> Both Deloisy and Rao have also featured epoxide opening in their formal synthesis of myriocin.<sup>68-69</sup> Chida *et al.* took D-mannose and constructed the quaternary centre using an Overman rearrangement in a 7:1 ratio of diastereomers. The most recent synthesis, by Marsden and Jones features the synthesis of a quaternary (*E*)-vinylglycine using an asymmetric deconjugative alkylation of a dehydroamino acid, with complete diastereoselective control. The subsequent dihydroxylation also proceeded with excellent diastereoselectivities, yielding a 90:10 mixture of diastereomers. These two key reactions allowed not only the synthesis of (+)-myriocin, but also its analogue 2-*epi*-myriocin.<sup>70</sup>

To date there have only been a limited number of total syntheses of the mycestericins (**24-30**), with the main interest in the diastereomeric pairs mycestericin D/E (**27/28**) and F/G (**29/30**). The sole total synthesis of (–)-mycestericin A **24** is by Chida *et al.* in which the Overman rearrangement is utilised to allow access to the key stereochemistry required (Scheme 9). This methodology is also applied to the synthesis of 14-*epi*-mycestericin A<sup>71-72</sup>, myriocin **23**<sup>73</sup> and other sphingosine analogues such as lactacystin<sup>74-75</sup> and sphingofungin E<sup>76</sup>).

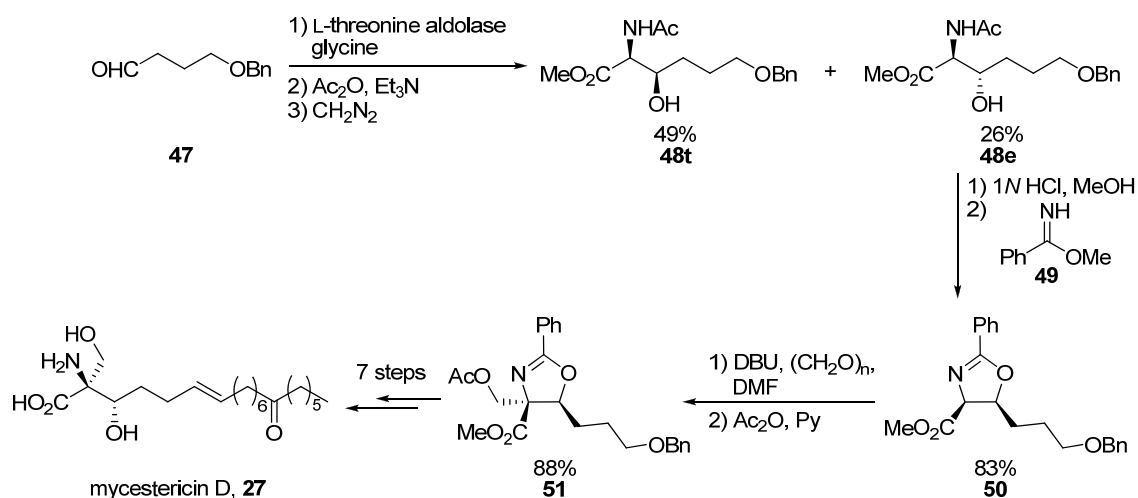


**Scheme 9 - The Overman rearrangement in the synthesis of mycestericin A**

Starting from dimethyl L-tartrate **43** the acetonide **44** was formed over 8 steps, with the penultimate step a Wittig reaction installing the *E*-alkene as a single isomer. Treatment with trichloroacetonitrile and DBU afforded the trichloroacetimide **45**, which was used without any further purification. The subsequent Overman rearrangement proceeded after heating to  $140^\circ\text{C}$  in xylene in the presence of potassium carbonate. After 48 hours the desired trichloroamide **46** was formed in 62% yield, along with its epimer *epi*-**46**. The desired compound **46** was then used to complete the total synthesis in a further 15 linear steps.

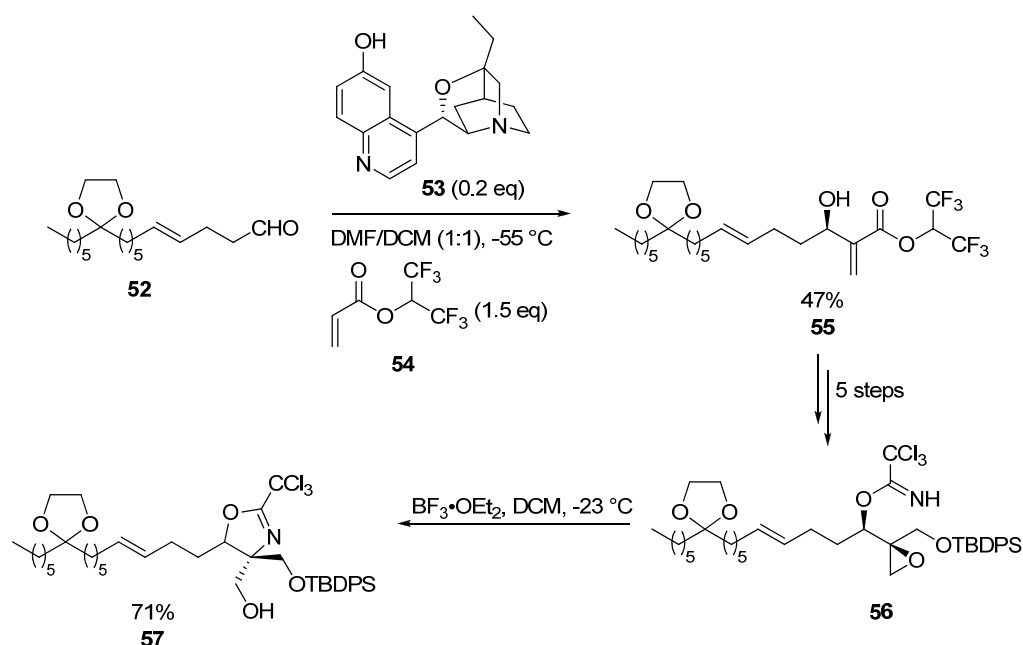
Whilst there are currently no syntheses for either mycestericin B or C (**25** and **26** respectively), (–)-mycestericin D **27** has been synthesised using an L-threonine aldolase catalysed aldol reaction of glycine with 4-benzyloxybutanol (Scheme 10).<sup>77-78</sup> This aldol reaction gave mixed ratios of the *threo*- and *erythro*- $\beta$ -hydroxy- $\alpha$ -amino acids depending on the reaction time. The *erythro* isomer was the major product when reaction times were kept short (90:10 after 5 mins – albeit with a low yield of 18%, compared with 40:60 favouring the *threo* isomer after 15 hours, in 70% yield). A compromise was made between selectivity and yield settling on a 68:32 *erythro:threo* ratio, with a 75% yield. In order to affect separation of these diastereoisomers, protection by acetylation of the amino group and subsequent methylation of the carboxylic acid afforded the separable derivatives **48e** and **48t**. The enantiomerically pure *cis*-oxazoline **50** was formed in 83% yield, prior to treatment with

paraformaldehyde and DBU, followed by acetylation to stereoselectively produce the desired acetate **51** in 88% yield.



**Scheme 10 - L-Threonine aldolase catalysed synthesis of mycestericin D**

The synthesis of mycestericin D was completed in 7 steps. The formal synthesis of mycestericin F **29** was also presented, since the catalytic hydrogenation of a natural sample of **27** has been previously reported by Fujita *et al.* to give mycestericin F **29**.<sup>50</sup>

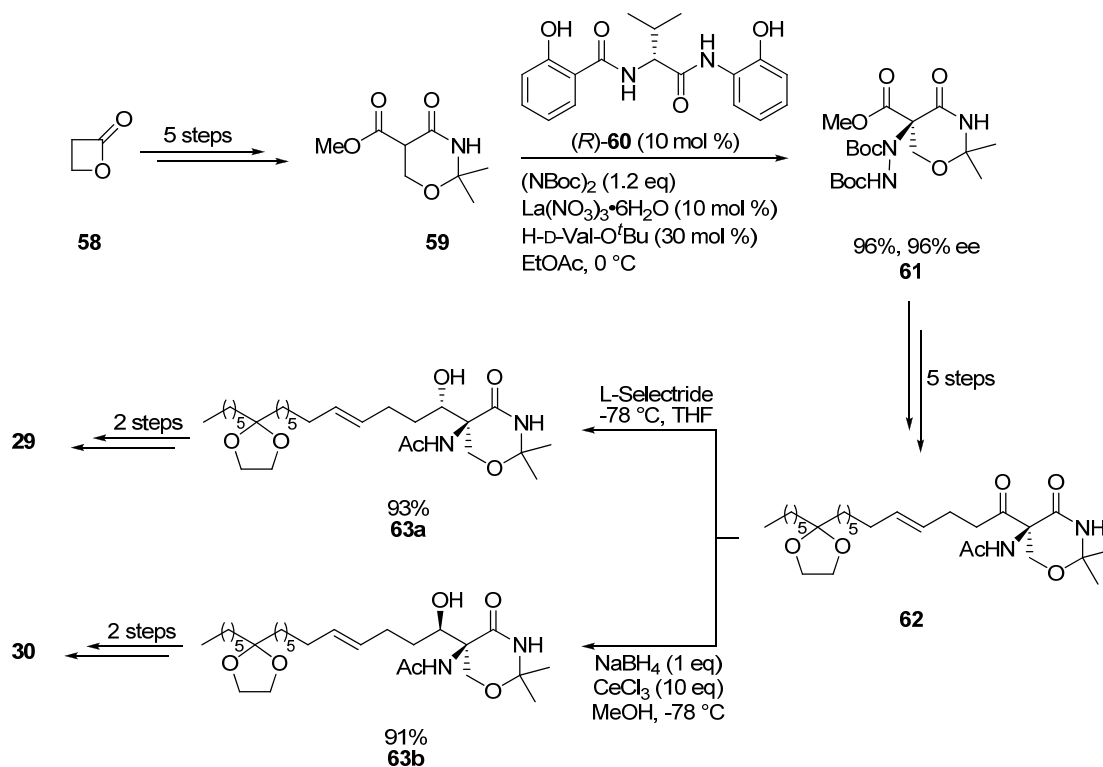


**Scheme 11 - Hatakeyama's approach towards the synthesis of mycestericin E**

The first reported total synthesis of the mycestericins E and G (**28** and **30**) was by Fujita *et al.* using a stereoselective acylation based on Seebach's self regeneration of

stereocentres as the key step in forming the quaternary centre.<sup>79-80</sup> Hatakeyama *et al.* approached the synthetic challenge of **28** via a *cinchona* alkaloid-catalysed asymmetric Baylis-Hillman reaction and a Lewis acid-promoted cyclisation of an epoxytrichloroacetimidate **56** as their key steps (Scheme 11).<sup>81</sup> With oxazoline **57** in hand a further 5 steps was required to complete the synthesis of (-)-mycestericin E **28** with an overall yield of 4.7% starting from the achiral aldehyde **52**.

Shibasakai *et al.* used a lanthanum/amide-based ligand system for an asymmetric amination as their key step in the synthesis of diastereomers mycestericin F and G (**29** and **30**).<sup>82</sup>



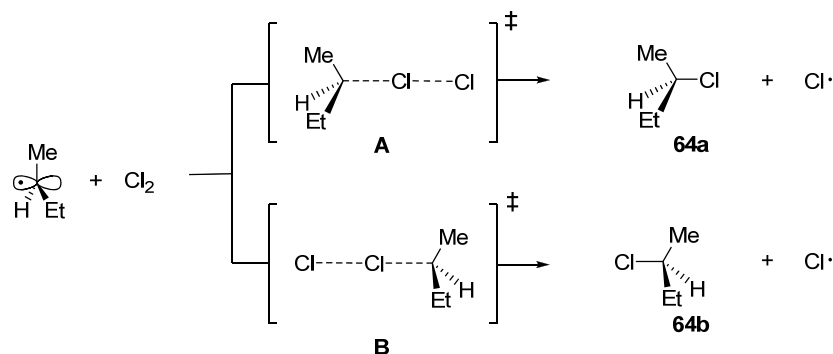
Scheme 12 - Shibasaki's synthesis of mycestericin F and G

After many unsatisfactory attempts at performing the catalytic asymmetric amination, and from previous studies, Shibasaki came to the conclusion that a *trans*-N-H proton as seen in the lactam type compound **59** was required for a successful reaction. Stable under both acidic and basic conditions, **59** isn't amenable to  $\beta$ -elimination. Consequently the amination proceeded smoothly at room temperature. Decreasing the temperature to 0 °C further improved the transformation, affording **61** in 96% yield and 96% ee. With the aliphatic tail installed, conditions were found to effect the

diastereoselective reduction to both **63a** and **63b**, in both cases with complete stereocontrol. The total syntheses were completed by catalytic hydrogenation followed by acid hydrolysis, to afford mycestericin F and G (**29** and **30**) in 10% and 11 % overall yield respectively.

### 1.3 Self-Regeneration of Stereocentres

One of the foundations of organic chemistry rests on the concept that a reaction involving an achiral molecule with a prochiral trigonal centre at the site of reactivity will result, if none of the reactants or surroundings are chiral, in the formation of a statistical mix of enantiomeric products. That is, a racemic molecule will be produced. Even if the intermediate is radical, or anionic, and has a trigonal-pyramidal geometry it will be capable of rapid inversion – especially in acyclic systems.<sup>80</sup>



Scheme 13- Transition states associated with an  $\text{S}_{\text{N}}1$  reaction.

Take the example of the *sec*-butyl free radical reacting with chlorine (Scheme 13). The reaction can take place on either side of the molecule, with the relative rates of the two competing reactions the same. Indeed, the two transition states **A** and **B** are enantiomeric, leading to identical physical properties; including bond angles, lengths and also the free energies of formation. Because of this, the energy of activation will be identical with a 50:50 mixture of (*R*)- and (*S*)-2-chlorobutane (**64a** and **64b**) being formed (Figure 8).<sup>83</sup>

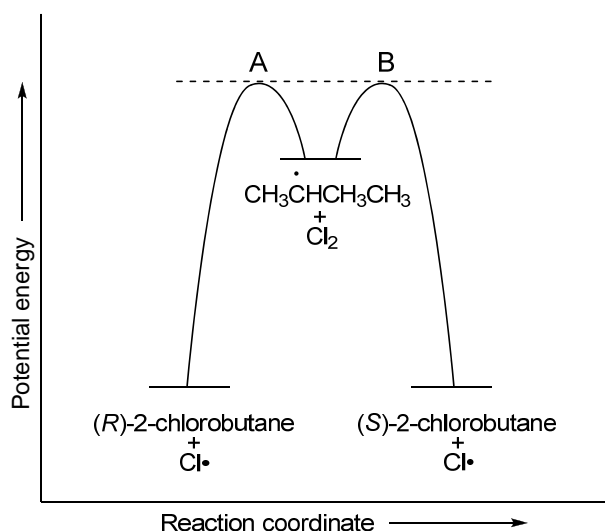
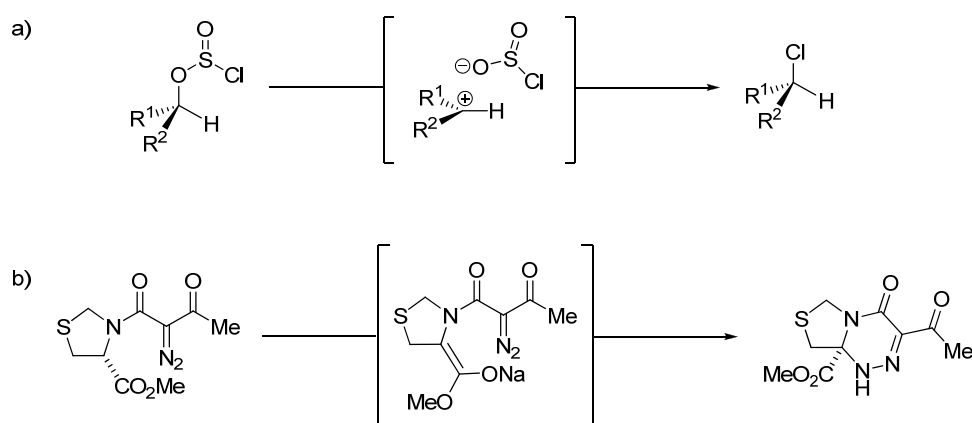


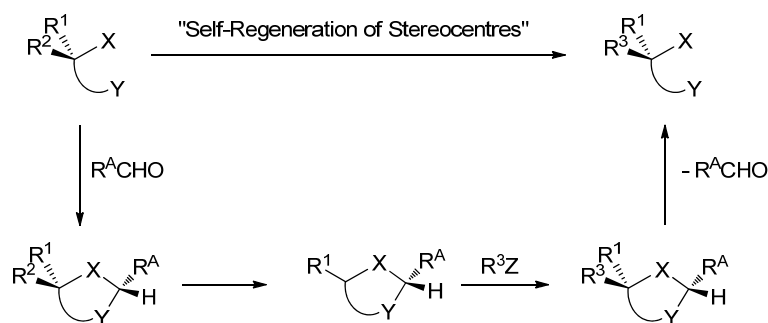
Figure 8 - An achiral intermediate gives enantiomeric transition states with equal activation energies<sup>83</sup>

There are examples which, on the face of it, appear to contradict this rule. The  $S_N1$  substitution of a hydroxyl group with chlorine using thionyl chloride is one illustration of this (Scheme 14a).<sup>84</sup> In this case, the ion pair does not completely dissociate before the concomitant loss of sulphur dioxide to allow the nucleophilic attack of the chloride on the same face. There are even examples of enolates, whereby the only centre of chirality is destroyed, which provide exceptions to the rules. Some of these cases can be ascribed to suitably stable enolate intermediates which possess axes of chirality (Scheme 14b), whilst others can form aggregates with chiral components in the reaction mixture.<sup>85-86</sup>



Scheme 14 - Retention of stereochemistry. a) Decomposition of alkyl chlorosulphites in an  $S_N1$  manner.<sup>84</sup> b) Stereoselective trapping of an enolate by a diazooxoketo group with retention of stereochemistry<sup>85</sup>

With the aim to incorporate readily available, simple, chiral compounds into complex target molecules, Dieter Seebach developed a method of producing inherently pro-chiral enolates of  $\alpha$ -amino or  $\alpha$ -hydroxy acids which would nonetheless react with electrophiles in a manner that afforded enantiomerically enriched products. This straightforward but widely applicable principle is known as the self-regeneration of stereocentres (SRS) (Scheme 15).<sup>87-90</sup>



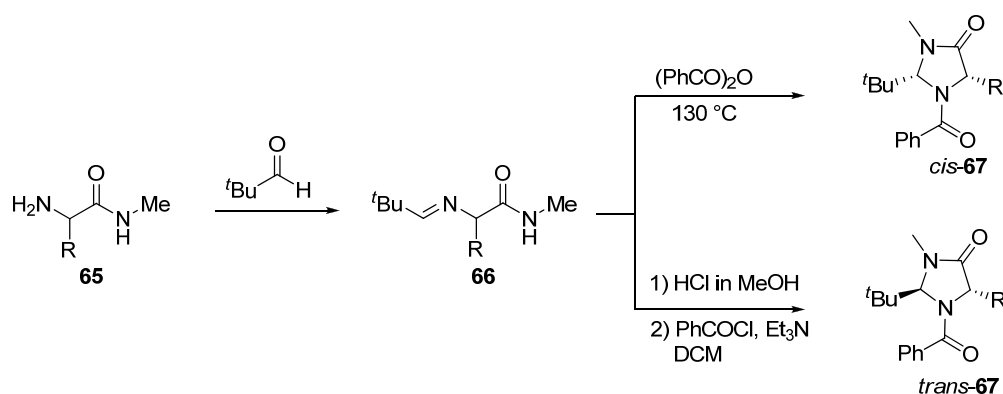
**Scheme 15 - The principle of self-regeneration of stereocentres.**

SRS follows a highly simple process: the chiral starting material must possess two functional groups capable of forming an acetal (or equivalent functional group), and contain a single chiral centre. Acetal formation must occur stereoselectively, as the original stereogenic centre is lost during the creation of the intermediate trigonal centre. The ensuing reaction with the intermediate is performed diastereoselectively due to the existence of chirality in the temporary acetal moiety. The final stage of the process is removal of the acetal leaving the desired product which has undergone a “dissociative, enantioselective substitution at a centre of chirality without the need for a chiral auxiliary”.<sup>80</sup> Whilst obviously requiring an auxiliary in the form of the aldehyde, the simplicity and ingenuity of this principle is that it is not a chiral auxiliary, but a common, cheap and readily available aldehyde that simply utilises the original chirality present in the starting material.

### 1.3.1 Endocyclic Enolates in SRS

The twenty proteinogenic amino acids and their related  $\alpha$ -hydroxy acids, along with other similar natural compounds of this class, provide a substantial set of chiral building blocks which can be utilised in synthesis using SRS.

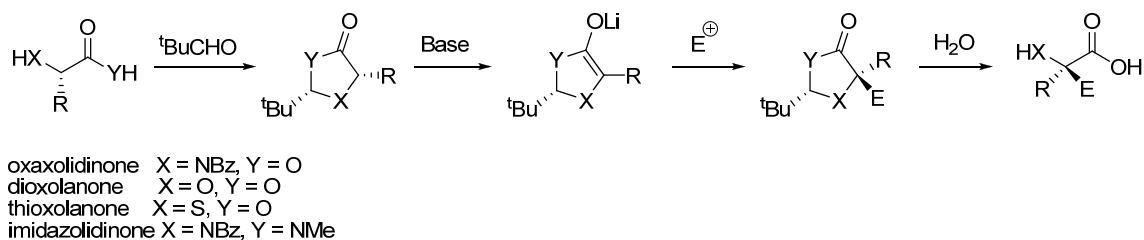
The acetalisation of  $\alpha$ -amino-,  $\alpha$ -hydroxy- and  $\alpha$ -sulphonylcarboxylic acids generally results in the thermodynamic synthesis of the *cis*-substituted oxazolidinone, dioxolanone and thioxolanone.<sup>91</sup> Furthermore an imidazolidinone can be synthesised from a relevant amino acid amide **65**, again under thermodynamic control yielding the *cis*-isomer *cis*-**67**. However, under kinetic control it is also possible to synthesise the *trans*-imidazolidinone *trans*-**67**, allowing access to either enantiomeric product from the naturally occurring amino acids (Scheme 16).<sup>92</sup> Pivalaldehyde is the preferred choice of auxiliary, for several reasons. Primarily, the bulky *t*Bu group affords excellent diastereoselectivity in both formation of the acetal and subsequent reactions at the newly created trigonal centre. Secondly, it creates an unobtrusive singlet in the <sup>1</sup>H NMR spectra which doesn't overlay with any other key spectral areas, and thirdly, it is a readily available reagent.



Scheme 16 - Synthesis of *cis*- and *trans*-2-(*tert*-butyl)-3-methylimidazolidin-4-ones

With the transient chiral centre now in place the reactive centre can be created. The favoured method for this is using LDA or LHMDS to form the lithium enolate, which can subsequently react with a range of electrophiles (Scheme 17). The imidazolidinone enolates are typically stable at temperatures above  $0\text{ }^\circ\text{C}$ , whereas those of the dioxolanones must be kept at low temperatures. The high diastereoselectivity of the reactions are due to the bulky *tert*-butyl group at the acetal centre shielding one face of the enolate, and therefore preventing any reaction with an electrophile from that face.

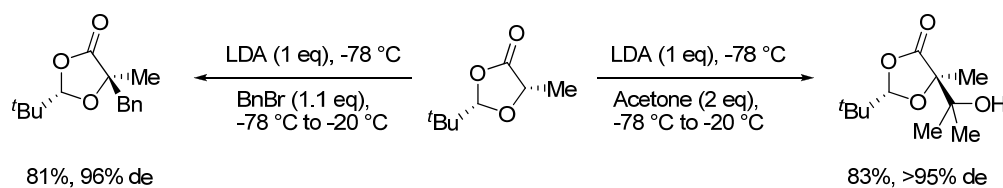




**Scheme 17 -  $\alpha$ -Alkylation of  $\alpha$ -amino,  $\alpha$ -hydroxy and  $\alpha$ -sulphonylcarboxylic acids and their derivatives using SRS**

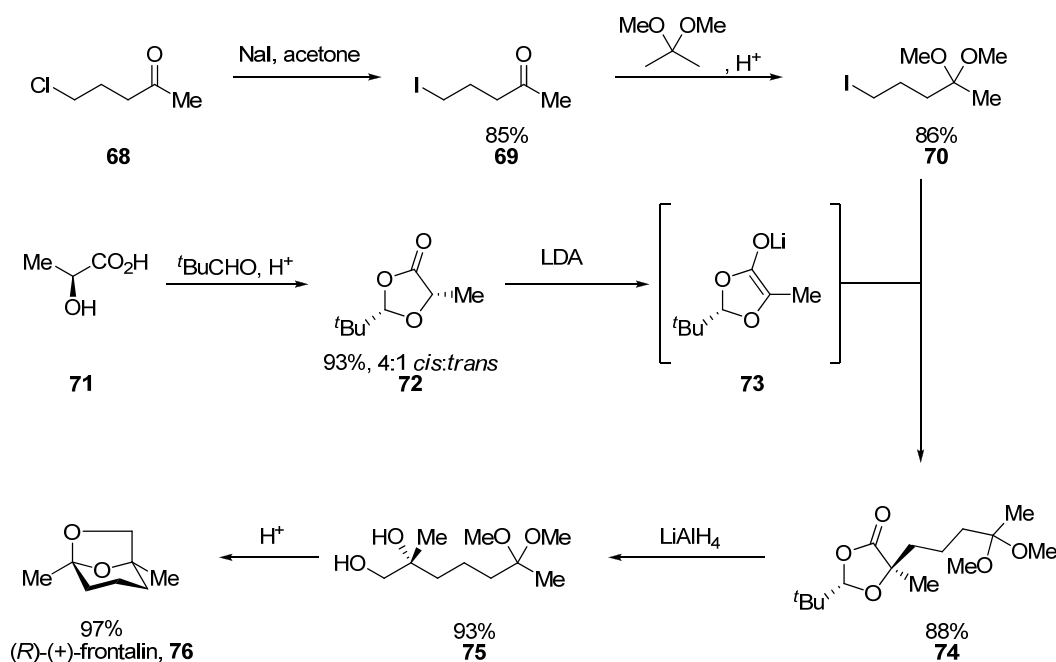
The final step in the process is hydrolysis to furnish the  $\alpha,\alpha$ -disubstituted carboxylic acid. Due to the stability of the new stereocentre it is possible to submit the alkylation products to fairly forcing conditions without fear of racemisation.

Whilst typical electrophiles are alkylation reagents, where the only new stereocentre is formed at the trigonal centre, symmetrical ketones have also been used (Scheme 18). However, the enolate generated has also been used in aldol reactions and with unsymmetrical ketones or aldehydes, which introduces a new chiral centre.<sup>93</sup> Seebach found that moderate to high levels of diastereoselectivity were possible for both aromatic and aliphatic aldehydes and unsymmetrical ketones, and that the same pattern observed with alkylations is followed, in that the *t*-butyl group controls the facial selectivity.



**Scheme 18 – Benzylation and reaction with acetone of a dioxolanone through an endocyclic enolate**

The use of SRS with endocyclic enolates has seen use in a variety of total syntheses, the first of which was reported by Seebach *et al.* in 1983 for the total synthesis of (+)- and (–)-frontalin in 5 linear steps and an overall yield of 73% starting from lactic acid (Scheme 19).<sup>94</sup>



Scheme 19 - Total synthesis of (R)-(+)-frontalin.

With *cis*-**72** isolated cleanly, the enolate was reacted with iododimethoxypentane **70** to afford the alkylated product **74** as a single diastereomer. The synthesis of (+)-frontalin was completed in a further 2 steps

There are many more complex and involved syntheses, such as the synthesis of (+)-eremantholide (Figure 9).<sup>95</sup> The first step in the synthesis is the reaction of the same lactic acid enolate **73** with 2,3-dibromopropene, creating a key stereocentre that is maintained throughout the rest of the synthesis, which included a novel use of the Ramberg-Bäcklund sequence to effect a medium-sized ring contraction. SRS is also used in the total synthesis of (+)-indicine *N*-oxide by Yamada *et al.* where by a stereochemical illustration was put forward for the outcome of the aldol reaction between the dioxolanone and acetaldehyde (Scheme 20).<sup>96</sup>

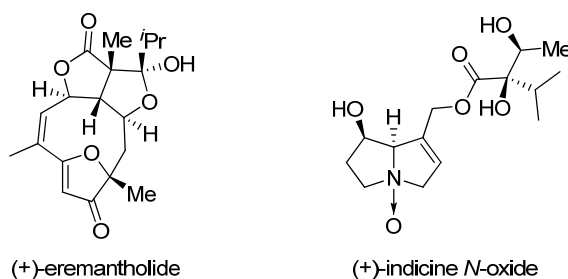
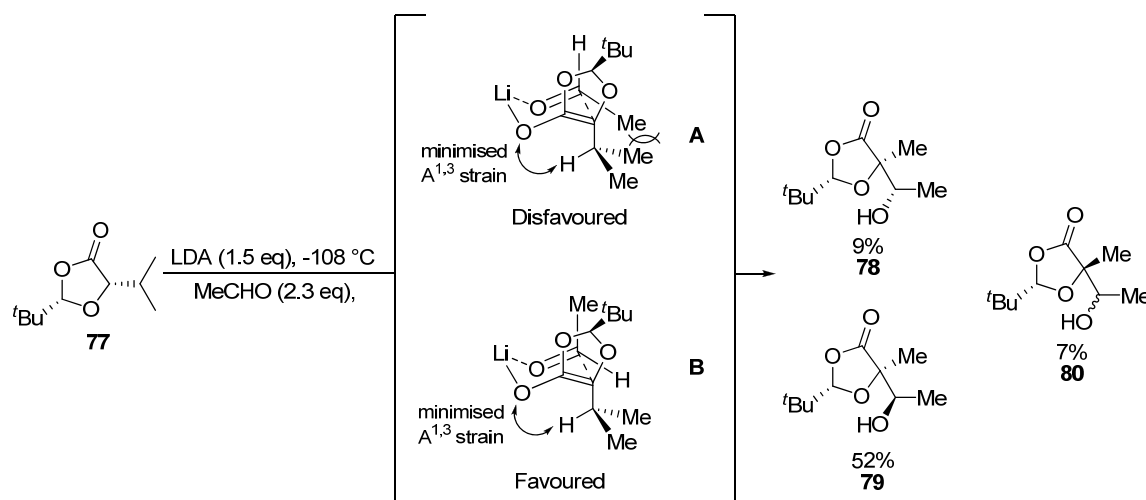


Figure 9 – Natural products synthesised using SRS.

In this instance, once 1,3-allylic strain has been minimised, and approach of the acetaldehyde is considered to be opposite to the *tert*-butyl group, there are two possible transition states. Transition state **A** features a large steric interaction between the acetaldehyde and the *iso*-propyl group of the dioxolanone. This interaction is no longer present in transition state **B**, and as a result is favoured leading to lactone alcohol **79** in a 52% yield. Yamada also saw a small amount of product **80** resulting from approach of the aldehyde on the same face as the bulky *tert*-butyl group. However, the desired lactone alcohol **79** was isolatable from its diastereomers after repeated chromatography.



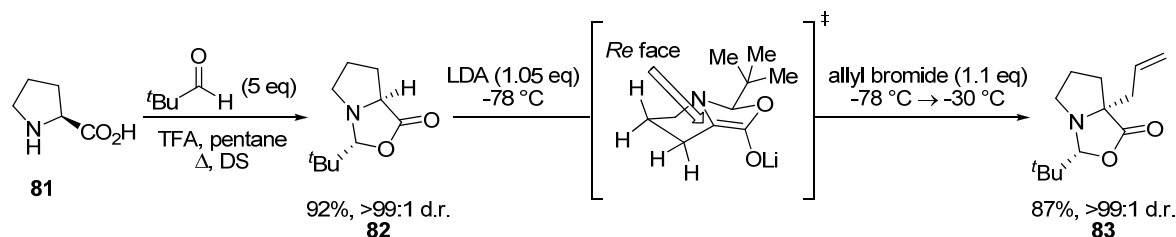
Scheme 20 -Diastereoselectivity seen in the synthesis of (+)-indicine *N*-oxide

### 1.3.2 Bicyclic Enolates in SRS

Another application of the SRS principle is the formation of a bicyclic acetal, with subsequent enolisation and then either alkylation, or aldol reaction. This approach has been favoured by many, including Seebach, and has been used in the total synthesis of brevianamide B by Williams *et al.* (Scheme 22), whilst Baldwin *et al.* used a highly erudite refinement of the SRS principle in the total synthesis of (+)-lactacystin (Scheme 23).<sup>97-98</sup>

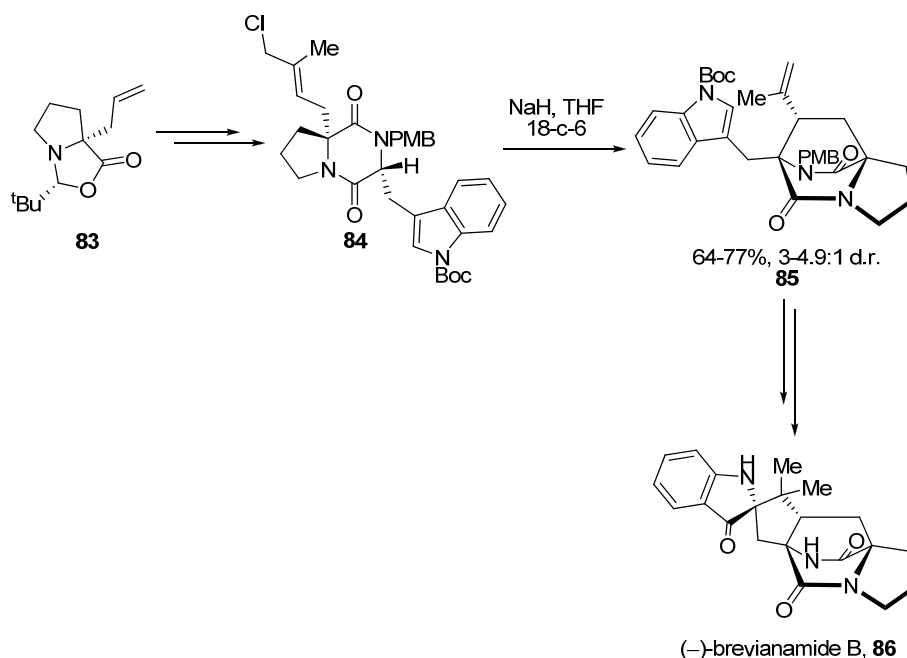
Williams *et al.* used allylated proline derivative **83**, previously reported by Seebach, as the starting point for the synthesis of brevianamide B (Scheme 21).<sup>88</sup> The condensation reaction between proline and pivalaldehyde yields a single isomer of the *N,O*-acetal **82**. Subsequent LDA promoted enolisation and reaction with allyl bromide furnished the  $\alpha$ -

substituted proline derivative **83** as a single diastereomer. Selectivity is due to approach of the electrophile on the *re* face, leaving the electrophile *cis* to the *tert*-butyl group, on the *exo* side of the 1-aza-3-oxabicyclo[3.3.0]octane system. This is in contrast to the *anti* selectivity prevalent in the mono-endocyclic enolates discussed previously. This demonstrates the efficiency of the SRS principle, such that it can be used as the formal starting material in the total synthesis of natural products.



Scheme 21 - *Re* facial selectivity in the allylation of a bicyclic *N,O*-acetal

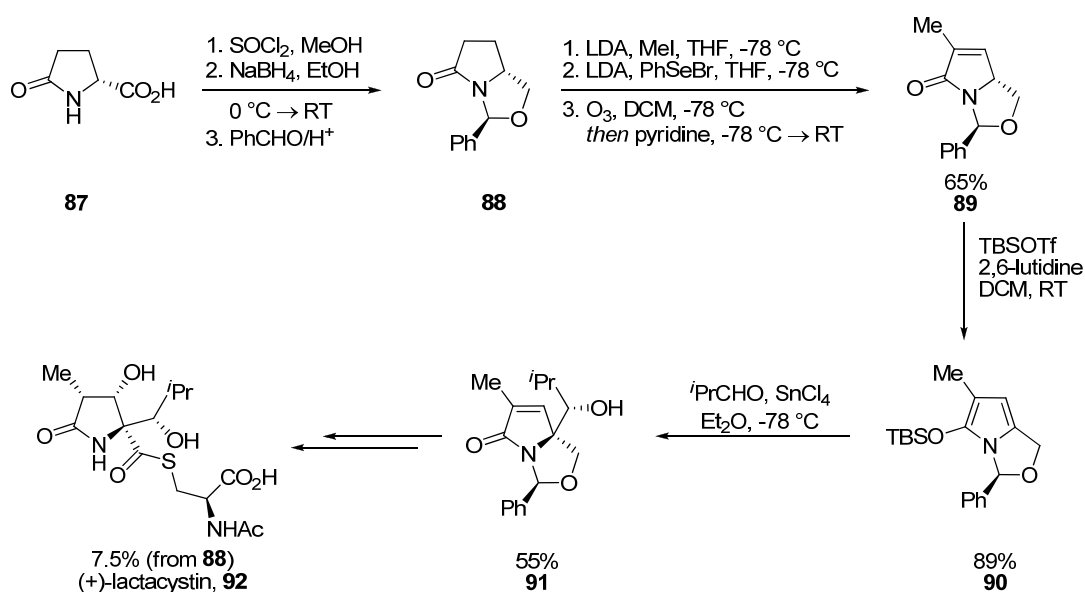
Further derivatisation by Williams led to the formation of allylic chloride **84** that was then subjected to the key stereoselective intramolecular  $S_N2'$  cyclisation which provided the remaining stereogenic centre necessary for the completion of brevianamide B.



Scheme 22 - Total synthesis of (-)-brevianamide B.

Baldwin's synthesis of lactocystin featured an aldol reaction between isobutyraldehyde and a bicyclic siloxypyrrole. The bicyclic oxazolidine **88** was prepared from (*R*)-

glutamic acid **87** in three steps following previously reported procedures.<sup>99-100</sup> Next followed a sophisticated series of elaborations to yield the unsaturated derivative **89** using methylation and selenenylation/ozonolysis. Finally, treatment with TBSOTf and 2,6-lutidine afforded the key siloxypyrrole **90**. An aldol reaction led to a 9:1 mixture of diastereomers, however, after chromatography the major isomer **91** was isolated in 55% yield. Further derivitisation led to (+)-lactacystin **92** in an overall yield of 7.5% (from **88**)



Scheme 23 – Baldwin's total synthesis of (+)-lactacystin

### 1.3.3 Exocyclic Enolates in SRS

All the previous examples of SRS have involved enolates formed within the cyclic structure. However, it is possible, and indeed desirable, to form a system that allows an exocyclic enolate to be created whilst retaining the principles of SRS.

It is practical to protect 2,3-diaminopropanoic acid, serine, cysteine and glyceric acid as seen in Figure 10.

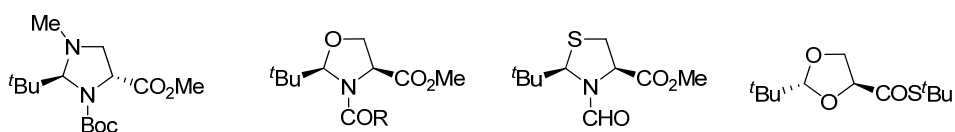
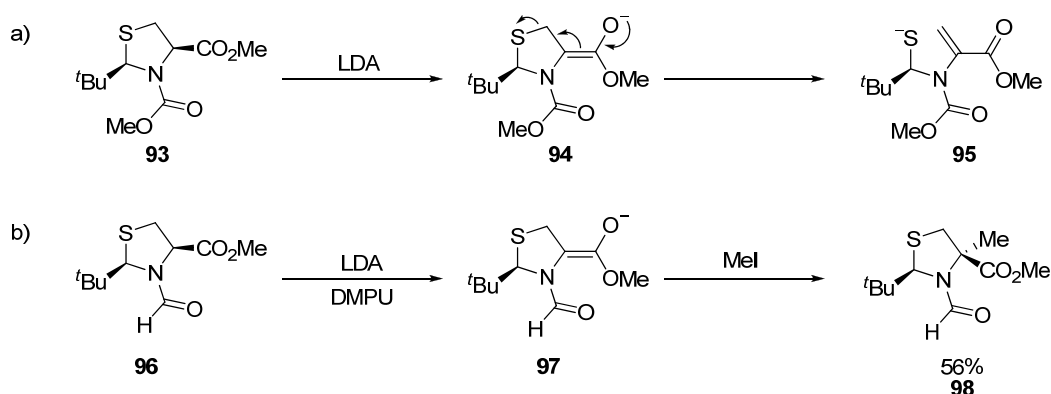


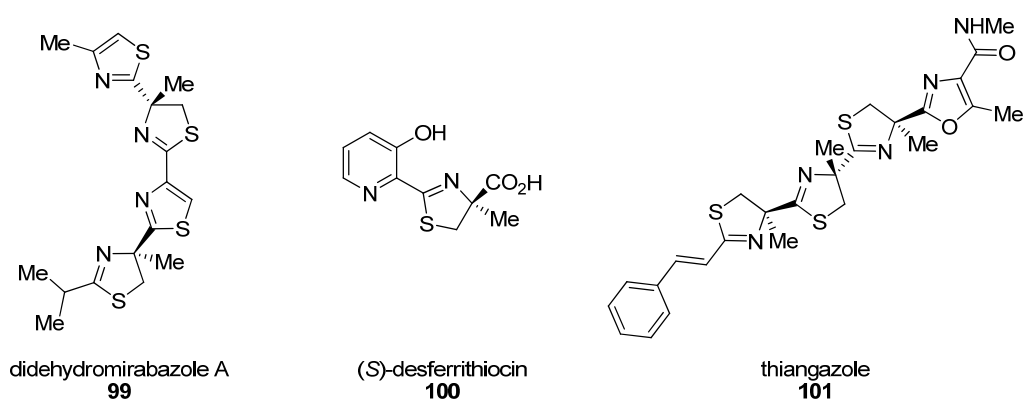
Figure 10 - Protected forms of 1,3-diaminopropanoic acid, serine, cysteine and glyceric acid

Treatment with a lithium base allows formation of an exocyclic enolate, which, despite the presence of an endocyclic  $\beta$ -leaving group, is relatively stable. This stability isn't however absolute, and in the case of cysteine the character of the *N*-acyl group is paramount to its stability; only the enolate formed for the formyl derivative **96** is stable enough to undergo alkylation (Scheme 24).<sup>101-103</sup>



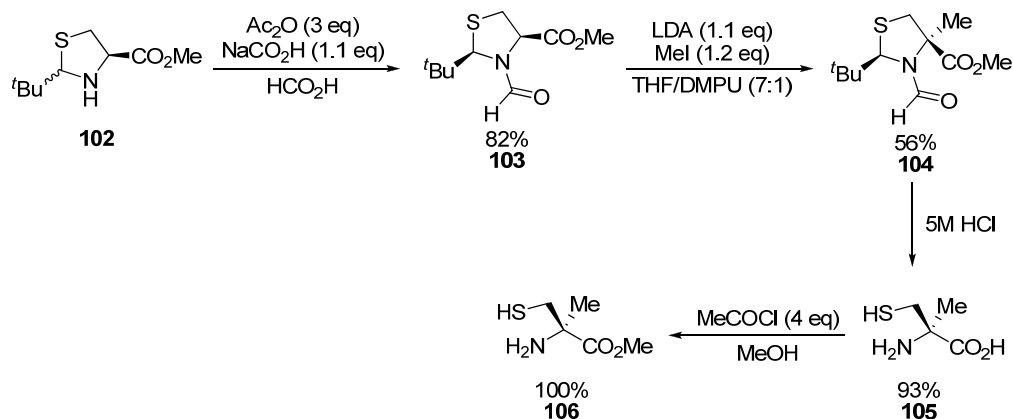
**Scheme 24 - a) *N*-ester derivative undergoes facile  $\beta$ -elimination. b) *N*-formyl derivative successfully undergoes alkylation**

Pattenden *et al.* have made use of these *N*-formyl thiazolidines in the total synthesis of many natural products, such as didehydromirabazole A **99**; a cytotoxic alkaloid, and (*S*)-desferrithiocin **100**; a ferric ion chelator (Figure 11).<sup>102, 104-106</sup> One of their targets, thiagazole **101**, shows a 100% inhibition of HIV-1 at 4.7 pM, along with no cell toxicity.<sup>107</sup> Furthermore, it is able to discriminate between HIV-1 and HIV-2.



**Figure 11 - Didehydromirabazole A, (*S*)-desferrithiocin and thiagazole**

These three natural products are all derived from either (*R*)- or (*S*)-2-methylcysteine, or indeed, feature core segments derived from both. It was essential for these total syntheses that a suitable large-scale synthesis of this chiral building block was achieved.



Scheme 25 - Large-scale synthesis of (*R*)-2-methylcysteine

Thiazolidine **102** was derived from (*R*)-cysteine methyl ester hydrochloride and pivalaldehyde. After formylation, a single diastereomer **103** was formed, allowing for stereoselective alkylation using LDA in the presence of DMPU. This methylated thiazolidine **104** had an exclusive *anti* relationship between the methyl and *tert*-butyl groups. Acid hydrolysis furnished the (*R*)-2-methylcysteine **105**, which, for use in the total synthesis was methylated and used as methyl ester **106**.

As is seen for the endocyclic enolates, high levels of diastereocontrol are seen in the exocyclic derivatives. The control provided can be explained using stereochemical models (Figure 12).<sup>90</sup>

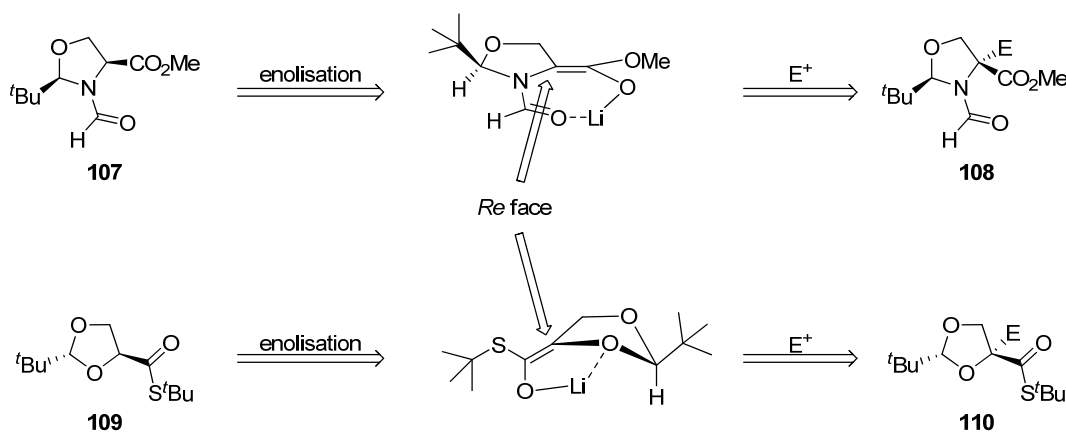
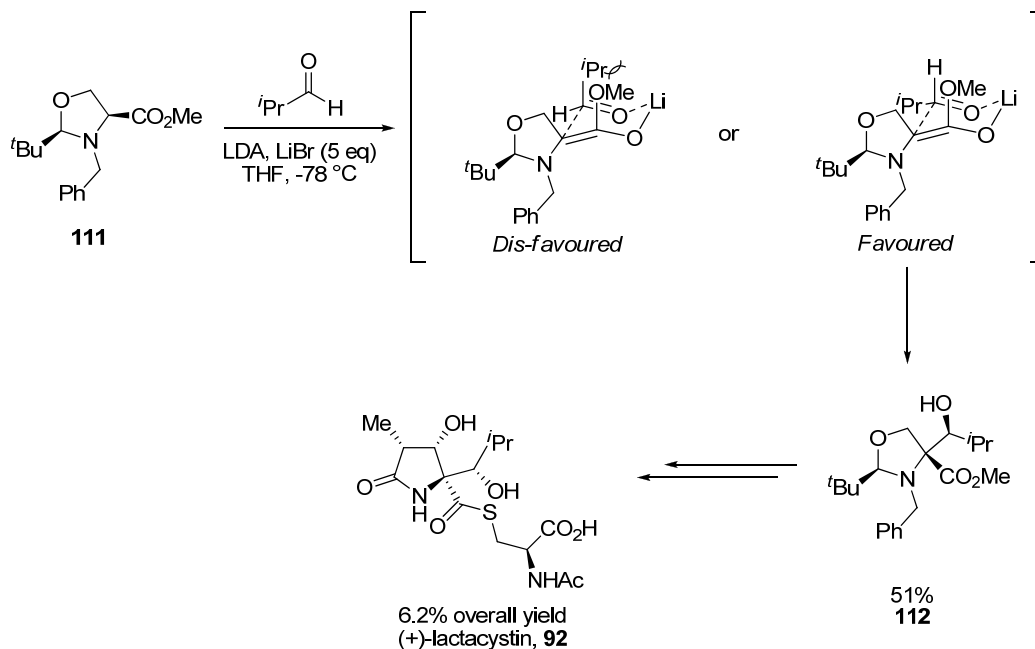


Figure 12 - Stereochemical model of exocyclic enolates in SRS

The *N*-formyl oxazolidine **107** forms a planar enolate, with the electrophilic attack occurring opposite the bulky *tert*-butyl group giving rise to the *trans*-oxazolidine **108**. However, the dioxolane ring **109** is puckered on enolisation allowing the *tert*-butyl group to be equatorial. Now, the dioxolane ring, and the *S*-*tert*-butyl group are shielding the bottom face of the enolate, hence accounting for the more unusual *cis*-stereochemistry seen in **110**.

Whilst there are many examples of the use of alkylations and aldol reactions with exocyclic enolates, their use in total synthesis is more limited. However, Corey *et al.* demonstrated its potential in the synthesis of lactacystin (Scheme 26).<sup>108</sup> *N*-Benzylserine was used as the chiral starting material to synthesise oxazolidine **111**. This was deprotonated using LDA with the lithium enolate-lithium bromide complex reacting with isobutyraldehyde to afford the enantiomerically pure aldol product **112** in 51% yield after recrystallisation. It is worth noting that, in the absence of lithium bromide, poor yields and selectivities were seen. The synthesis was completed in a further 13 steps with an overall yield of 6.2%.

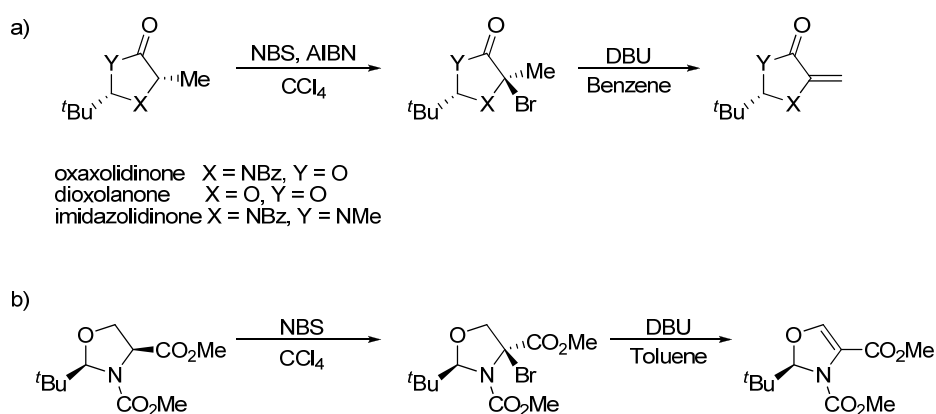


Scheme 26 - Corey's total synthesis of (+)-lactacystin



### 1.3.4 $\alpha,\beta$ -Unsaturated Carbonyl Compounds in SRS

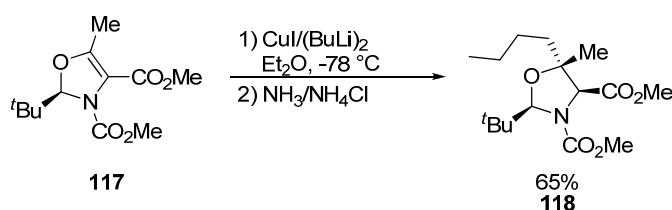
It is also possible to add new substituents at the position  $\beta$  or  $\gamma$  to the carbonyl in addition to those at the  $\alpha$  position seen in the previous sections. The same five membered acetals are prepared using an aldehyde and the prerequisite chiral starting material. These resulting compounds can then be brominated using a radical process that shows a preference for the C-H bond adjacent to the carbonyl group over the acetal centre. Elimination of HBr then leads to an exocyclic double bond in the case of dioxolanones, imidazolidinones and oxazolidinones (Scheme 27a) and endocyclic double bonds for oxazolidine and thiazolidine substrates (Scheme 27b).



**Scheme 27 - Preparation of chiral  $\alpha,\beta$ -unsaturated carbonyl compounds**

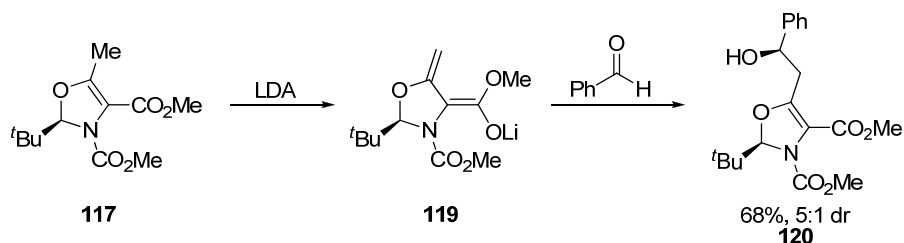
These unsaturated compounds are now amenable to a variety of processes, such as the Michael addition of nucleophiles, addition of radicals, and cycloadditions. In some cases, it is also possible to react with electrophiles *via* the formation of dienolates.

The oxazoline **117** derived from threonine presents the opportunity for reaction at both the  $\beta$ - and the  $\gamma$ -position. Michael addition allows creation of a new quaternary centre as a single diastereomer, in a good yield (Scheme 28).<sup>109</sup>



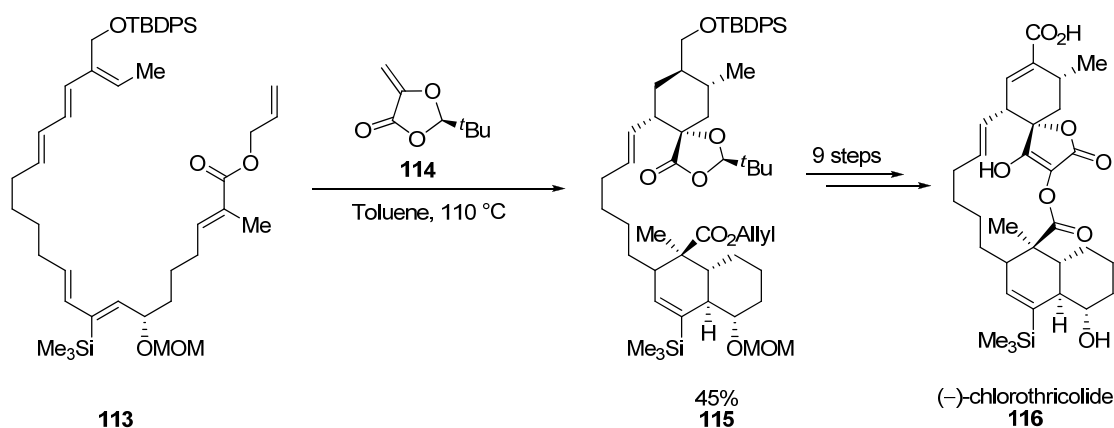
**Scheme 28 - Michael addition of a nucleophile to an  $\alpha,\beta$ -unsaturated carbonyl compound**

Rather than react the oxazoline with a nucleophile, it is also possible for it to undergo  $\gamma$ -deprotonation to form the dienolate **119**. It will now act as a nucleophile itself and reaction with benzaldehyde proceeds with a high regioselectivity, along with good yields and diastereoselectivity.<sup>109</sup>



**Scheme 29 - Dienolate formation and reaction with benzaldehyde**

Roush *et al.* have used SRS with a Diels-Alder approach in the total synthesis of (–)-chlorothricolide.<sup>110</sup> With proof of principle showing that high diastereoselectivities can be obtained, this was applied to the final synthesis in a challenging tandem inter-intramolecular Diels-Alder reaction under reflux in toluene for 20 hours. HPLC analysis of the reaction mixture showed four predominate cycloadducts, in a ratio of 67:13:10:10. This closely matched the expectations drawn from previous separate attempts; with 93:7 observed for the *intermolecular* reaction<sup>111</sup>, and 72:19:9 selectivity for the intramolecular reaction.<sup>112</sup>



**Scheme 30 - Tandem inter-intramolecular Diels-Alder reaction in the synthesis of (–)-chlorothricolide**

## 1.4 Pericyclic Reactions

Pericyclic reactions occur through a concerted mechanism *via* a cyclic transition state.<sup>113</sup> During pericyclic reactions no intermediates are formed, nor is there any change in formal charge. There are four main classes of pericyclic reactions: cycloadditions, electrocyclic reactions, group transfer reactions and sigmatropic rearrangements (Figure 13).

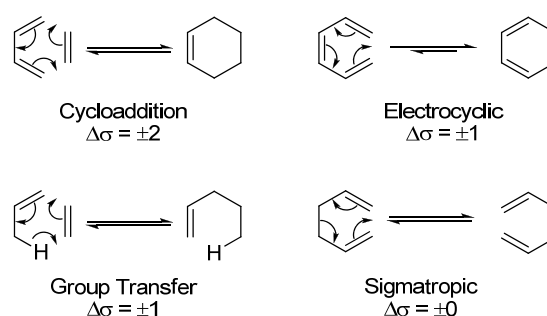
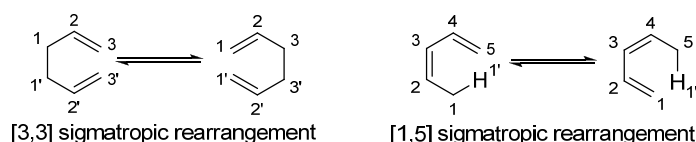


Figure 13 - Examples of pericyclic reactions

Pericyclic reactions are described according to the change in  $\sigma$ -bonds in the system. Cycloadditions; such as the well known Diels-Alder sees the formation or loss of two  $\sigma$ -bonds, electrocyclic reactions have a change of one  $\sigma$ -bond, whilst sigmatropic rearrangements see the migration of a single  $\sigma$ -bond, with no change in the number of  $\sigma$ -bonds. Group transfer reactions are similar to sigmatropic rearrangements in that  $\sigma$ -bond migration is observed. However, the process is bimolecular, and forms one new  $\sigma$ -bond, and is hence classified as a separate entity.

### 1.4.1 Sigmatropic Rearrangements

In a sigmatropic reaction a single  $\sigma$ -bond migrates from one location in a molecule to another. They are assigned a numerical [i,j] classification referring to the number of atoms that each sigma terminus has moved. An example of a [3,3] sigmatropic rearrangement is the Cope rearrangement, whilst the rearrangement of 1,3-pentadiene is an example of a [1,5] sigmatropic rearrangement (Figure 14).

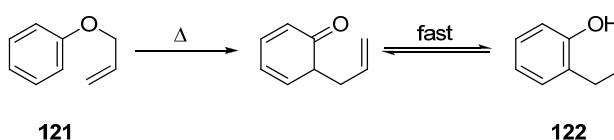


**Figure 14 - Numbering of an [i,j] Sigmatropic Rearrangement**

The numbering system starts from either side of the bond being broken or formed. In a sigmatropic rearrangement the molecular formula of the starting material is retained, hence complete atom economy is achieved.

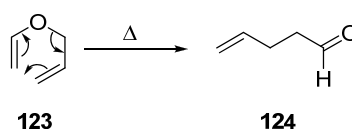
### 1.4.2 Claisen Rearrangement

The Claisen rearrangement was the first example of a [3,3] sigmatropic rearrangement. Published in 1912, Rainer Ludwig Claisen showed that heating an allyl aryl ether **121** produced allyl phenols **122** without any intermediates (Scheme 31).<sup>114</sup> The Claisen rearrangement is often referred to in the literature as a 3-oxa-Cope rearrangement, despite the fact that the first Cope rearrangement wasn't reported until 1940, 28 years after Claisen's seminal paper.<sup>115-116</sup> The Claisen rearrangement, as a "suprafacial, concerted, nonsynchronous pericyclic process", is occasionally considered as an intramolecular S<sub>N</sub>2 alkylation.<sup>117</sup>



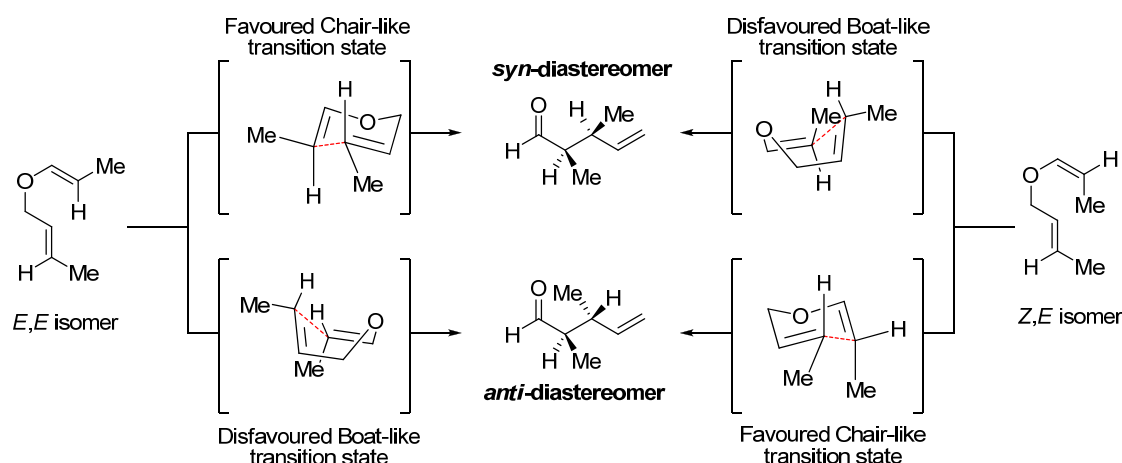
### Scheme 31 – The aromatic Claisen rearrangement

There are two categories of the Claisen rearrangement, the aromatic Claisen rearrangement, the main focus of the seminal paper, and the aliphatic Claisen rearrangement, touched upon briefly in the first paragraph of Claisen's original paper. It is argued that it is the understated aliphatic Claisen rearrangement which has stimulated more interest from both a synthetic and mechanistic viewpoint. The aliphatic Claisen rearrangement proceeds after heating of an allyl vinyl ether **123** to around 200 °C, leading to the formation of  $\gamma,\delta$ -unsaturated aldehydes **124**.



Scheme 32 - The aliphatic Claisen rearrangement

Synthetically the Claisen rearrangement has found good use in total syntheses due to its high stereoselectivity, and is used in key steps of such syntheses. The rearrangement can proceed through two conformational types of transition states to produce opposite diastereomers (Scheme 33). As the transition states differ in energy, the ratio of products obtained reflects the transition state geometry. Schmid *et al.* has examined the stereochemistry (and rate) of the rearrangement, and found that all 4 of the conformational isomers he studied proceeded *via* the chair-like transition state.<sup>118</sup>

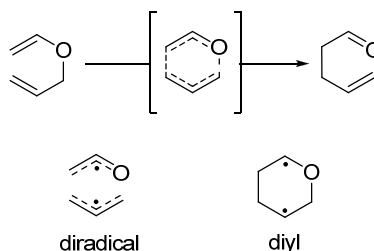


Scheme 33 - Transition States in the Claisen Rearrangement

Therefore the *E,E* and *Z,Z* isomers rearrange to yield the *syn* diastereomer, whilst both the *E,Z* and *Z,E* isomers afford the *anti* diastereomer.

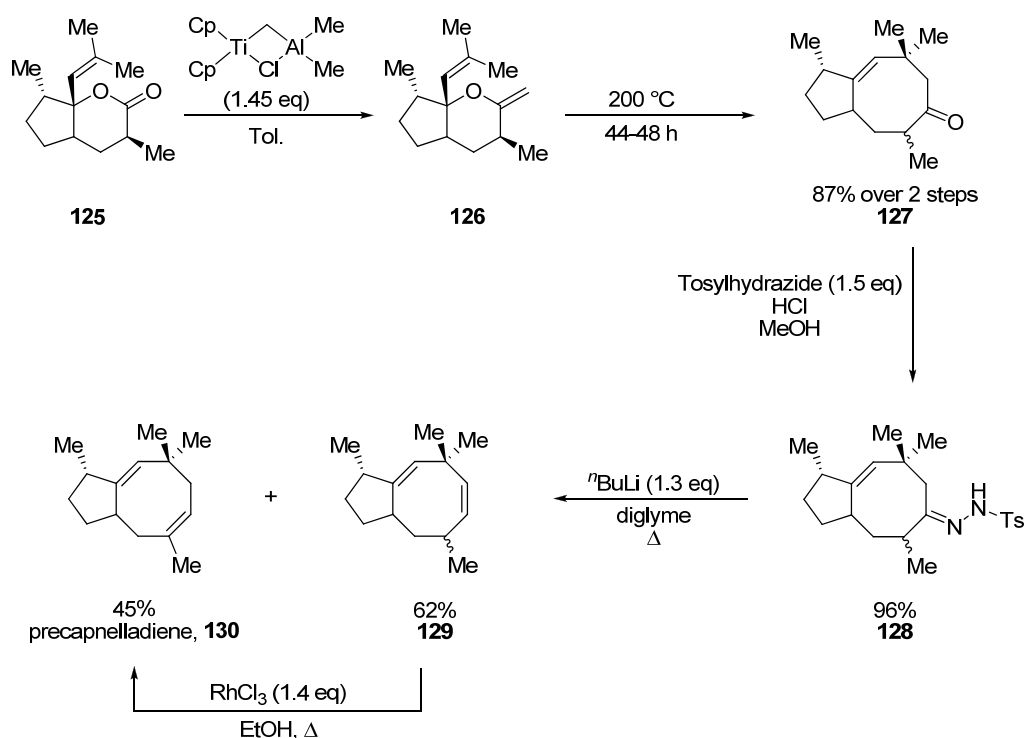
Hurd and Pollack first suggested a cyclic mechanism<sup>119</sup> whilst Gajewski and Conrad used secondary kinetic deuterium isotope effects to suggest an earlier, reactant-like transition state.<sup>120-121</sup> This more recent study suggested that the transition state had more bond-breaking than bond-making character, with the transition state more closely resembling the diradical as opposed to the 1,4-diyl (Scheme 34).

Early dissociative transition state with diradical character



**Scheme 34 - Nature of the transition state in the aliphatic Claisen rearrangement postulated by Gajewski and Conrad**

The Claisen rearrangement has found many uses in organic synthesis, with Paquette *et al.* employing it as their central strategy in the total synthesis of (±)-precapnelladiene **130** (Scheme 35).<sup>122</sup>

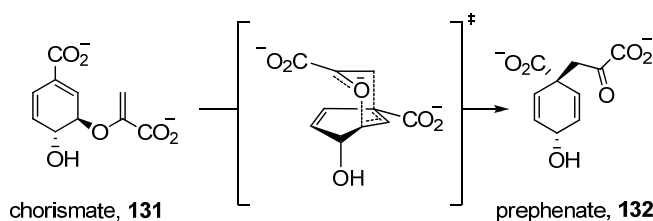


**Scheme 35 – Final steps in the total synthesis of precapnelladiene including a key Claisen rearrangement**

They completed the total synthesis in 11 steps, with an overall yield of 20% achieved starting from 8 $\alpha$ -methyl-bicyclo[3.3.0]octan-2-one. Conversion of lactone **125** to enol ether **126** via the Tebbe reagent, followed by the aliphatic Claisen rearrangement proceeded efficiently in 87% yield over the two steps. The synthesis was concluded by forming tosylhydrazone **128**, before allowing it to decompose under carbenoid conditions based on those developed by Friedman.<sup>123</sup> The resultant isomeric mixture

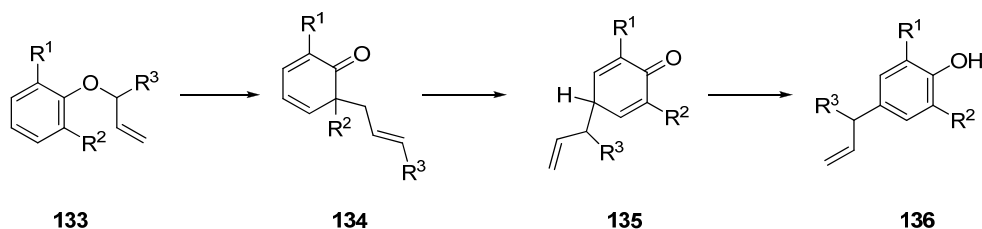
was separable by chromatography on silica gel infused with 2% silver nitrate. Subsequent isomerisation of **129** allowed final isolation of precapnelladiene **130**.

Nature also utilises the aliphatic Claisen rearrangement, in the enzyme-catalysed rearrangement of chorismate **131** into prephenate **132** (Scheme 36); a precursor for the essential amino acids tyrosine and phenylalanine.<sup>124</sup> Chorismate mutase is the key enzyme which is responsible for the rate enhancement of approximately one million fold compared to the uncatalysed (yet still facile) rearrangement.<sup>125</sup> This reaction, is one of the few pericyclic reactions in biology and has provided a rare opportunity for an understanding to be gained in how such transformations are promoted and accomplished in nature.



Scheme 36 - Enzyme catalysed rearrangement of chorismate into prephenate

The aromatic Claisen rearrangement (as seen in Scheme 31) sees the rearrangement of allylic aryl ethers to *o*-allylphenols on heating. In this rearrangement an allylic shift is seen for any substituent  $\alpha$  to the ether oxygen, whereby it will finish  $\gamma$  to the ring. If a proton is present in the *ortho* position then tautomerisation will follow, with the driving force being re-aromatisation of the ring.<sup>126</sup>

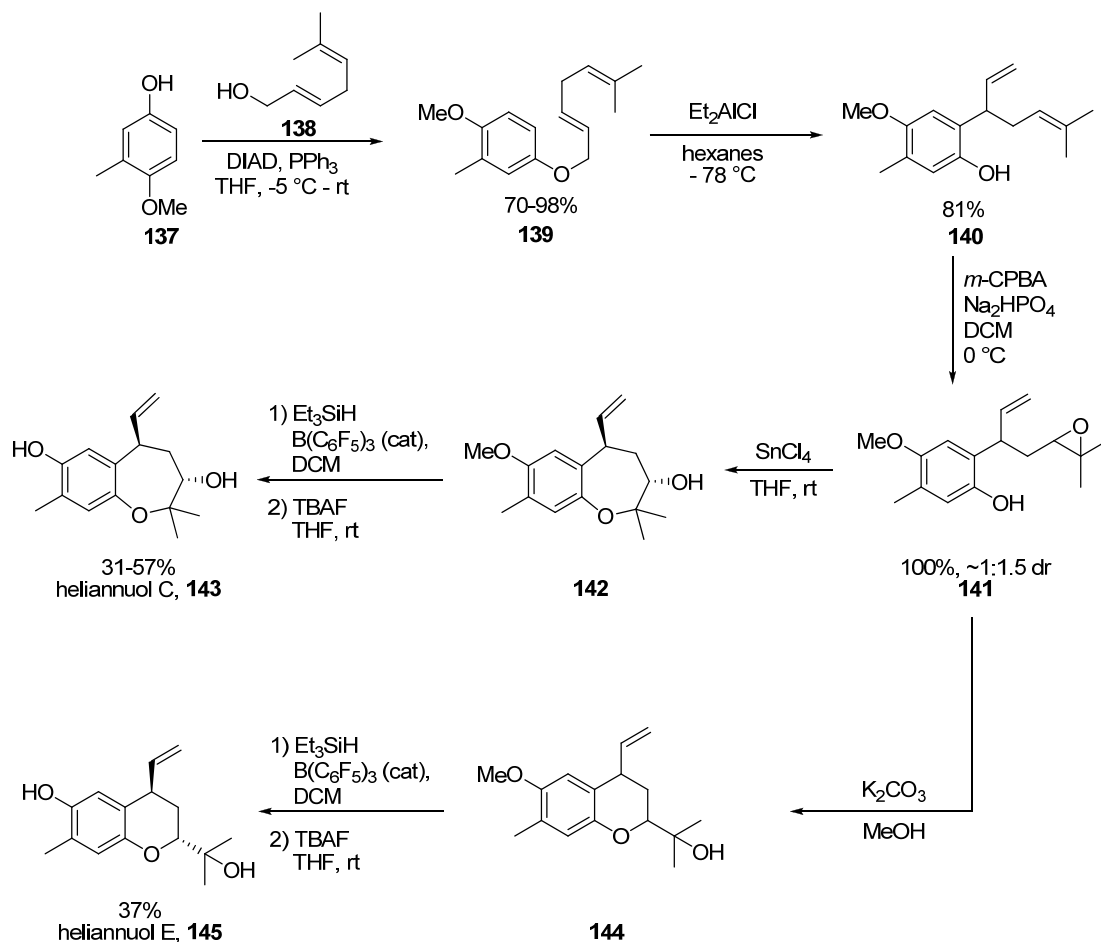


Scheme 37 - Secondary Cope rearrangement in the aromatic Claisen rearrangement

If both *ortho* positions on the ring are substituted (**133**), then re-aromatisation in this fashion is not possible. Instead, migration of the allylic group to the *para* position is

observed (**135**). This second [3,3] sigmatropic rearrangement is an example of the Cope rearrangement (Scheme 37).

As is seen for the aliphatic Claisen rearrangement, the aromatic version also finds widespread use in total syntheses. It was used by Vyvyan *et al.* in the total synthesis of (±)-heliannuol C and E, both in 7 steps, with overall yields of 15% and 9% respectively.<sup>127</sup> The heliannuols, extracted from *Helianthus annuus*, are a group of phenolic allelochemicals that are active against dicotyledon plant species.<sup>128</sup> This gives them the potential to be used in the agricultural industry for germination inhibition of crops such as lettuce and cress.



Scheme 38 - Total synthesis of (±)-heliannuol C and E

Aryl ether **139** required for the aromatic Claisen rearrangement was synthesised in good yield *via* Mitsunobu etherification (70-98%). The rearrangement itself proceeded regioselectively in high yield (81%) at low temperature. Epoxidation led to a mixture of



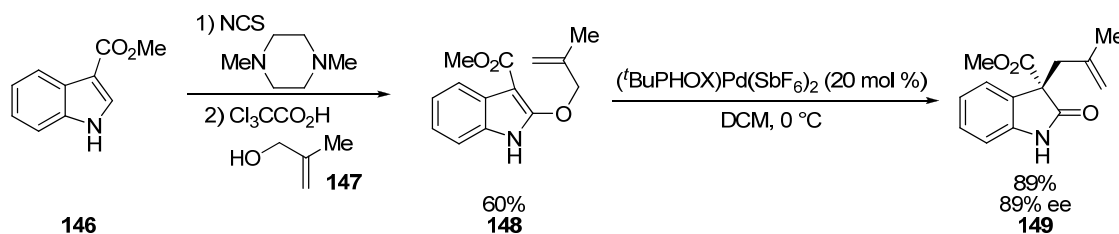
inseparable diastereomers with a quantitative yield (~1:1.5 dr), which was then used in both cyclization reactions. The first of these, a regioselective 7-*endo*-cyclization from treatment of the epoxide with SnCl<sub>4</sub> provided separable benzoxepanes, of which **142** was the correct diastereomer. Subsequent deprotection yielded heliannuol C **143**. Heliannuol E **145** was synthesised using a 6-*exo*-cyclization, to form **144** followed by demethylation. Use of a stronger base led to problems, with migration of the olefin into conjugation with the aromatic ring being observed. The same demethylation seen for heliannuol C was employed as the final step.

### 1.4.3 Variants of the Claisen Rearrangement

Since the initial publication of the Claisen rearrangement there have been many variations reported. Many of these now have their own sub-classes present in the literature. Some key examples of these include:

#### *Meerwein-Eschenmoser Claisen rearrangement*

In the Meerwein-Eschenmoser Claisen rearrangement 2-amino allyl vinyl ethers are transformed into  $\gamma,\delta$ -unsaturated amides.<sup>116</sup> First discovered in 1961 by Meerwein it was Eschenmoser *et al.* who first introduced a practical procedure for this rearrangement.<sup>129</sup> In 1964 they described the conversion of allylic and benzylic carbinols to ketene *N,O*-acetal intermediates, which then underwent facile [3,3] sigmatropic rearrangement.<sup>130-131</sup> The rearrangement of allenylic carbinol systems has also been reported.<sup>132</sup> The neutral conditions typically required allows the use of sensitive substrates, provided they are thermally stable.

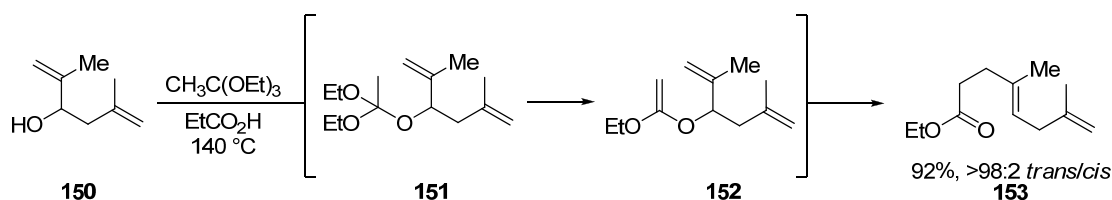


Scheme 39 - The first catalytic enantioselective Meerwein-Eschenmoser Claisen rearrangement

Kozłowski and Linton have recently described the first catalytic enantioselective rearrangement, using palladium(II) catalysis (Scheme 39).<sup>133</sup>

### Johnson-Claisen rearrangement

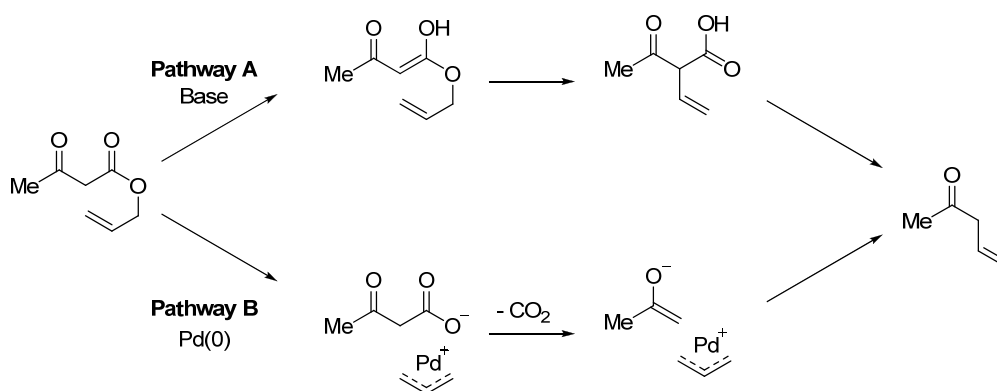
The Johnson-Claisen rearrangement is closely related to the Meerwein-Eschenmoser Claisen rearrangement, and proceeds *via* condensation of an *ortho*-ester and an allylic or propargylic alcohol.<sup>134-135</sup> The ketene acetal intermediate **152** rearranges through a [3,3] sigmatropic rearrangement to afford a  $\gamma,\delta$ -unsaturated ester **153**.



Scheme 40 - The Johnson-Claisen rearrangement

### Carroll rearrangement

There are two potential pathways through which the Carroll rearrangement can proceed. Both involve the [3,3] sigmatropic rearrangement of  $\beta$ -keto allylic esters into  $\beta$ -ketocarboxylic acids. Subsequent decarboxylation furnishes  $\gamma,\delta$ -unsaturated ketones.

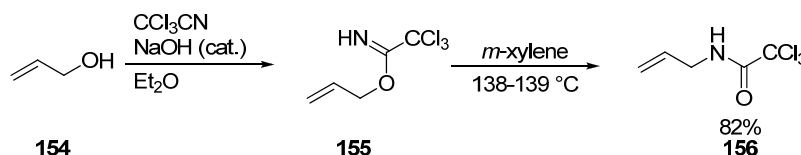


Scheme 41 - The Carroll rearrangement

The first pathway takes place in the presence of base with a high reaction temperature. The intermediate enol reacts in a Claisen rearrangement, with subsequent decarboxylation.<sup>136-137</sup> The second pathway is milder and proceeds through the use of palladium(0). In this route, an intermediate allyl cation/carboxylic acid anion organometallic complex is formed which undergoes decarboxylation and then addition into the  $\pi$ -allylic system.<sup>138</sup> By introducing suitable chiral ligands, this pathway allows the reaction to proceed in an enantioselective fashion.<sup>139</sup>

**Overman rearrangement**

The Overman rearrangement involves either the thermal, or transition metal catalysed rearrangement of allylic trichloroacetimidates to afford the corresponding trichloroacetamides.<sup>140</sup>

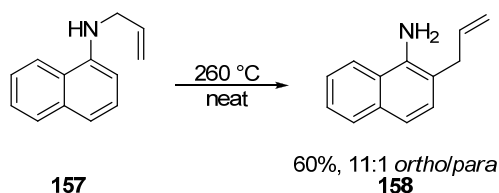


**Scheme 42 - The Overman rearrangement**

The allylic trichloroacetimidates are easily prepared by treating an allylic alcohol **154** with trichloroacetonitrile in the presence of catalytic amounts of base.

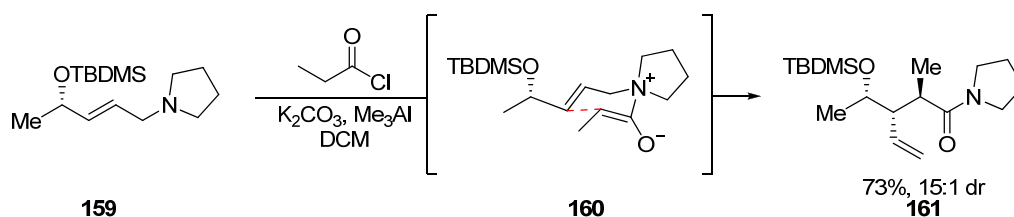
**Aza-Claisen rearrangement**

The aza-Claisen rearrangement sees the replacement of the oxygen atom in a Claisen rearrangement for a nitrogen atom. The rearrangement itself is a thermal process, and both aromatic and aliphatic substrates can be used. In the aromatic rearrangement some product distribution can be seen due to subsequent Cope rearrangement, similar to that seen in the Claisen rearrangement.



**Scheme 43 - The aza-Claisen rearrangement**

A major disadvantage of this rearrangement is the harsh conditions required. However, a zwitterionic aza-Claisen variant has been introduced, which allows for a reduction in temperature through the use of ammonium or amide enolates (Scheme 44).<sup>141-142</sup>



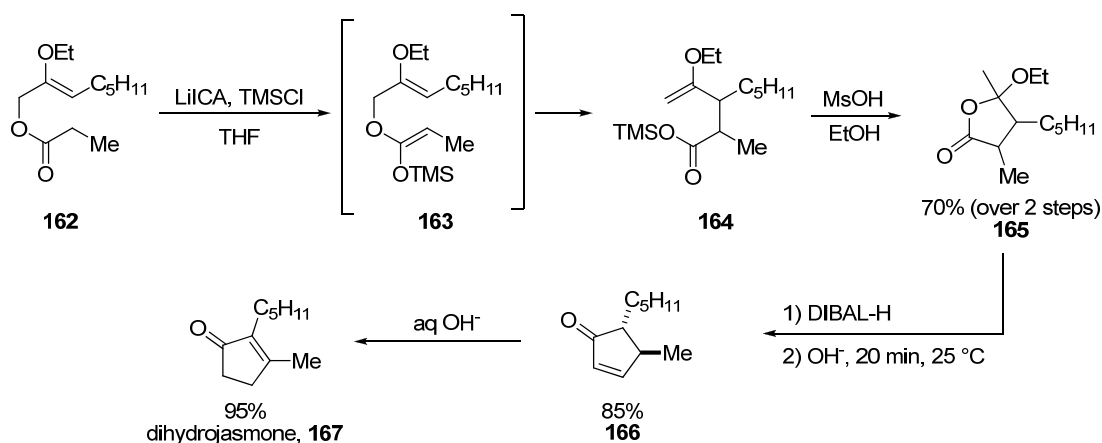
**Scheme 44 - The zwitterionic aza-Claisen rearrangement**

Treatment of allylamine **159** with propionyl chloride results in the formation of an acylammonium salt, which is deprotonated to generate the zwitterionic intermediate **160**. Subsequent [3,3] sigmatropic rearrangement generates the desired  $\gamma,\delta$ -unsaturated pyrrolidine amide **161** in good yield and excellent diastereoselectivity.

### 1.5 Ireland-Claisen Rearrangement

Introduced in 1972, the Ireland-Claisen rearrangement is a variant of the Claisen rearrangement. It is a [3,3] sigmatropic rearrangement of silyl ketene acetals formed from the enolization of allylic esters with a lithium dialkylamide base.<sup>143</sup> The resulting products are  $\delta,\gamma$ -unsaturated carboxylic acids. As with the Claisen rearrangement, it is used towards the synthesis of a diverse range of natural products. Whilst the first report of an ester enolate rearrangement was in 1937 by Tseou and Wang, this, and other scattered reports were beset with low yields and the need for high reaction temperatures.<sup>144-145</sup> Hence none had the success and potential synthetic application as the Ireland-Claisen rearrangement.

Ireland and Mueller were able to overcome these previously seen difficulties with the use of a lithium dialkylamide base. This allowed efficient enolization at low temperatures, whilst silylation of the ester enolate suppressed side reactions such as ketene decomposition and Claisen-type condensations. The applicability of the reaction was demonstrated in the synthesis of dihydrojasnone (Scheme 45).<sup>143</sup>

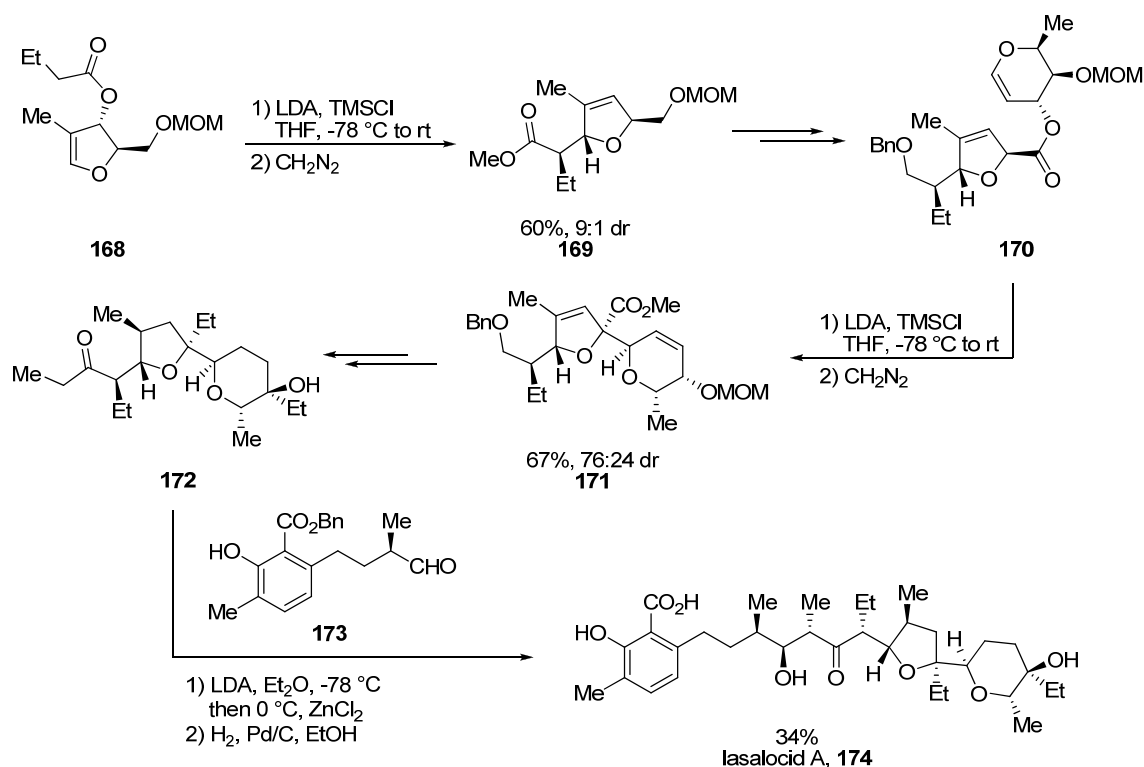


**Scheme 45 - Synthesis of dihydrojasmone incorporating the first example of the Ireland-Claisen rearrangement**

The synthesis of dihydrojasmone featured in Ireland's seminal paper saw lactone **165** produced in 70% yield from the allylic ester **162**. Subsequent reduction and then base treatment followed to yield the dihydrojasmone **167** with an overall yield of 57%.

The Ireland-Claisen rearrangement is a dynamic tool for the organic chemist due to the number of advantages it possesses. Such benefits include: ease of preparation of the allylic esters, allowing for facile access to the reaction substrates; control of the *E/Z* geometry of both the alkene and enolate, allowing for a high level of diastereoselectivity (*vide infra* 1.5.1 Diastereocontrol in the Ireland-Claisen Rearrangement); the high level of chirality transfer seen between the allylic stereocentre of the silyl ketene acetal and the newly formed stereocentres; and the ability to perform the reaction at low temperatures and under basic conditions. In essence, it is a more facile and synthetically viable reaction than the analogous Claisen rearrangement.

Ireland has demonstrated numerous total syntheses of natural products using the Ireland-Claisen rearrangement as one of the key steps.<sup>146-151</sup> In the synthesis of lasalocid A, two separate Ireland-Claisen rearrangements were employed with great success.



Scheme 46 - Total synthesis of lasalocid A

The initial rearrangement installed a tertiary centre  $\alpha$  to the furan oxygen. This resultant dihydrofuran **169** was transformed to furanyl pyran **170**. The second rearrangement, under the same conditions as previously used, produced the  $\alpha$ -carboxyl quaternary centre **171** with good diastereoselectivity and yield. Further elaboration led to ketone **172**, which was subsequently used in the aldol reaction with the previously prepared aldehyde **173**. Subsequent hydrogenation furnished the desired lasalocid A **174**.

### 1.5.1 Diastereocontrol in the Ireland-Claisen Rearrangement

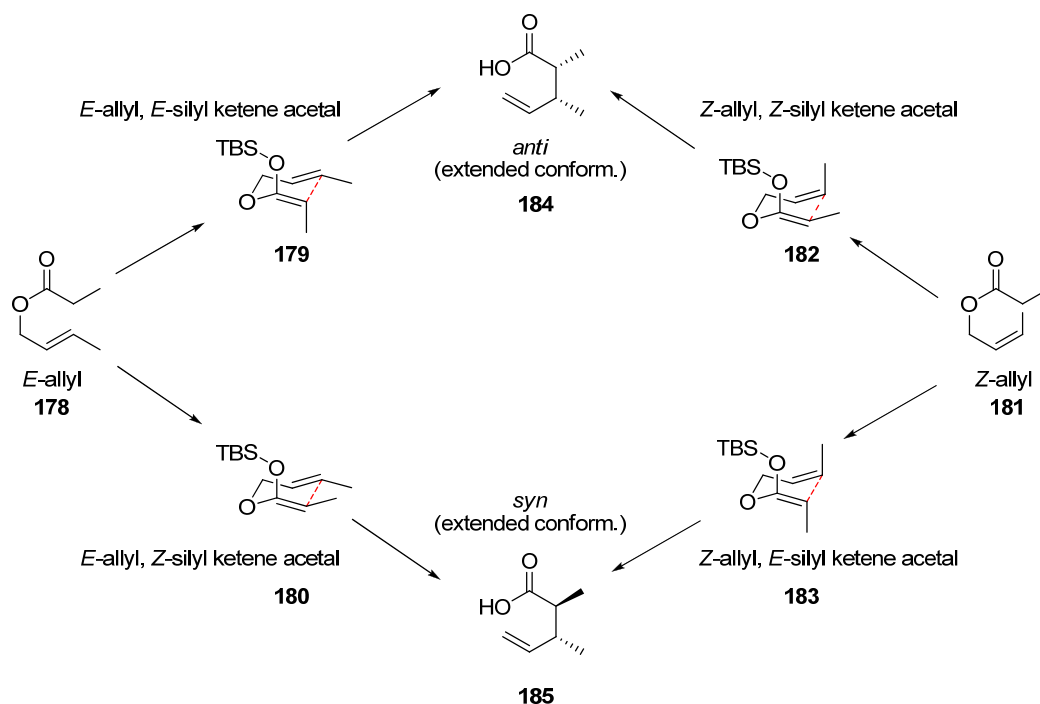
The Ireland-Claisen rearrangement proceeds *via* a highly ordered transition state. As a result of this, there is a preferential stereochemical outcome in favour of either *syn* (threo), or *anti* (erythro) pentenoic acids from pertinently substituted substrates. Such stereochemistry can be controlled by the geometry of the alkene, and that of the silyl ketene acetal. It is also dependant on the nature of the transition state – namely whether it proceeds *via* a chair-like or boat-like transition state. It is generally accepted that acyclic allyl silyl ketene acetals favour the chair-like transition state, whilst cyclic variants tend to prefer the boat-like structure.<sup>152-153</sup>

Whilst the control of the alkene geometry is dealt with during the substrate synthesis, the enolate (and hence silyl ketene acetal) geometry is developed *in situ*. Ireland reported that the ester enolate could be stereoselectively generated based on the character of the solvent used.<sup>154</sup> Subsequent trapping with a silyl agent (in this case TBSCl) produces the silyl ketene acetal. Due to changes in substituent priority between the ester enolate and the silyl ketene acetal, all geometries are assigned with respect to their silyl ketene acetal derivative. When THF was used as solvent, the *E*-silyl ketene acetal **176** was formed preferentially. However, on using a 23 vol% HMPA/THF mixture the *Z*-silyl ketene acetal **177** was preferentially obtained with the exception of phenyl acetates (Table 1).

Table 1 - Solvent control of silyl ketene acetals

Entry	R	R'	<i>E</i> / <i>Z</i> (THF)	<i>E</i> / <i>Z</i> (23 vol% HMPA, THF)
1	Et	Me	91:9	16:84
2	<sup>t</sup> Bu	Me	97:3	9:91
3	Et	<sup>t</sup> Bu	95:5	23:77
4	Ph	Me	29:71	5:95

With the ability to control the conformation of both the alkene and silyl ketene acetal, it is possible to predict the stereochemical outcome of rearrangements of acyclic silyl ketene acetals. As shown by Ireland, the *anti* 2,3-dimethyl pentenoic acid isomer **184** can be obtained in one of two ways: either by the rearrangement of the *E*-silyl ketene acetal of *E*-crotyl propionate **179**; or from the *Z*-silyl ketene acetal of the *Z*-crotyl propionate **182** with similar levels of diastereoselectivity. The corresponding *syn* 2,3-dimethyl pentenoic acid isomer **185** can be achieved from the *Z*-silyl ketene acetal of *E*-crotyl propionate **180**; or from the *E*-silyl ketene acetal of the *Z*-crotyl propionate **183**. Diastereoselectivities reported by Ireland ranged from 5:1 to 8:1 (Scheme 47).



### 1.5.2 Glycinates in the Ireland-Claisen Rearrangement

**Table 2 - Influence of *N*-protecting group on glycinate rearrangements**

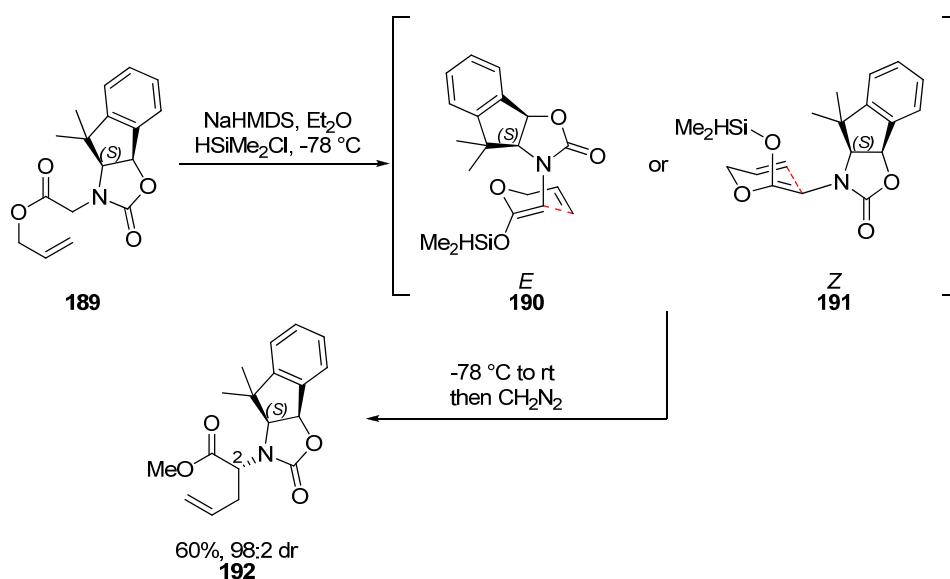
Entry	Substrate	R	R'	Yield (%)	dr
1	<b>186a</b>	Boc	H	60-65	9:1
2	<b>186b</b>	Cbz	H	65	4:1
3	<b>186c</b>	Bz	H	65	5.4:1
4	<b>186d</b>	TFA	H	58	1.5:1

The Ireland-Claisen rearrangement has been used in the synthesis of  $\alpha$ -amino acids by Bartlett and Barstow.<sup>155</sup> They explored a variety of *N*-protected crotyl glycinates (**186a-d**) using Ireland's optimized conditions<sup>152</sup> (2.1 eq LDA with 2.1 eq TMSCl added at -75 °C after 10 mins), and whilst both Cbz and benzoyl derivatives rearranged in



comparable yield, their diastereoselectivity was generally lower than that observed for the Boc analogue (Table 2).

Chiral glycinate have also been utilised in an approach by Saigo and co-workers to achieve absolute asymmetric induction.<sup>156</sup> The use of an aminoindanol auxiliary in allyl glycinate **189** in conjunction with the unusual silylating agent HSiMe<sub>2</sub>Cl produced a 98:2 diastereomeric ratio.



**Scheme 48 - Use of chiral glycinate in the Ireland-Claisen rearrangement**

It was postulated that the *E*-silyl ketene acetal **190** formed the chair conformation shown in order to minimise dipolar interactions. The allylic alkene can then rearrange from the less sterically congested face of the oxazolidine to yield the observed product **192**. However, based on previous precedent set by related carbamates, it is suggested that chelation favours the formation of a *Z*-silyl ketene acetal **191**.<sup>157-158</sup> Formation of the least sterically hindered conformation would also lead to the observed product (Scheme 48).

### ***Chelate Enolate Claisen Rearrangement***

The ester enolate Claisen rearrangement (the Ireland-Claisen rearrangement) found its success based on its ability to limit side reactions such as enolate decomposition. However, if heteroatoms with free electron pairs (such as oxygen, nitrogen, sulphur) are present as either  $\alpha$ - or  $\beta$ -substituted esters then chelation to the enolate metal is

possible, giving rise to five- (**193**) and six-membered (**194**) chelate rings respectively with high selectivities with respect to the *Z*-(*O*)-enolate formation (irrespective of HMPA addition) (Figure 15).

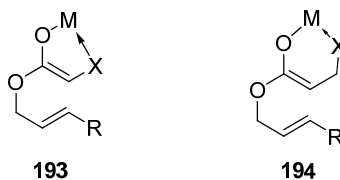
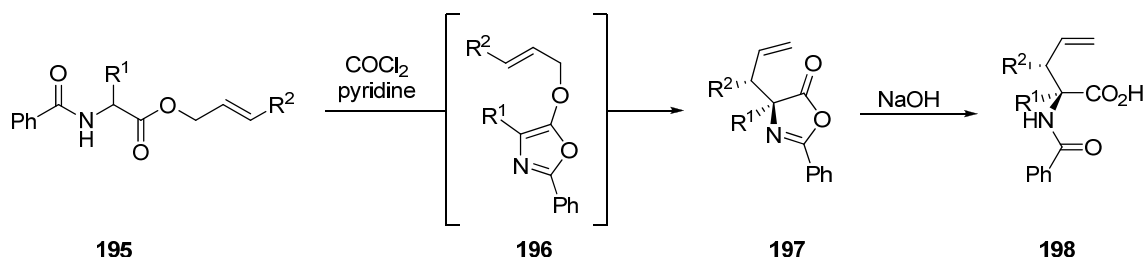


Figure 15 - Chelate enolates

The formation of the chelate results in the stabilisation of the enolate and therefore allows a direct rearrangement of the metal enolate.<sup>159</sup> Ireland's silylation and subsequent rearrangement is still possible too, albeit with the geometry set up by the chelated enolate.

When the allylic esters of *N*-protected amino acids undergo rearrangement,  $\gamma,\delta$ -unsaturated amino acids are attained. The first such synthesis was reported by Steglich *et al.* in 1975 (Scheme 49).<sup>160</sup> When *N*-benzoyl amino acid allylic esters **195** were treated with dehydrating agents (in this case phosgene) the oxazole intermediate **196** rearranged readily to the resulting allyloxazolinone **197**, with ensuing hydrolysis affording the  $\alpha$ -alkylated allylic amino acid **198**. As a result of the fixed geometry in the oxazole ring, a strong preference for the chair-like transition state is observed, with high diastereoselectivity seen as a consequence.



Scheme 49 - First synthesis of allylic amino acids by Ireland-Claisen rearrangement

Kazmaier has been prolific in the area of chelate enolate Ireland-Claisen rearrangements.<sup>159, 161-169</sup> In 1994 an investigation into the addition of several salts to the rearrangement of *N*-benzyloxycarbonylglycine crotyl ester **199** was conducted

(Table 3).<sup>166</sup> Rearrangement of the lithiated glycine allyl esters directly was unsuccessful, since the rearrangement itself occurs at temperatures at which the enolate decomposes. However addition of metal salts forms stable glycine enolate chelates which do not decompose upon warming to room temperature. Kazmaier found that copper(II) and nickel(II) salts formed such stable chelates that the corresponding enolates were not reactive enough to undergo the rearrangement (Table 3).

**Table 3 - Rearrangements of chelate-bridged glycine ester enolates in the presence of metal salts**

Entry	MX <sub>n</sub>	Yield (%)	dr ( <i>syn:anti</i> )
1	ZnCl <sub>2</sub>	90	95:5
2	CoCl <sub>2</sub>	78	93:7
3	MgCl <sub>2</sub>	85	91:9
4	Al(O <sup><i>i</i></sup> Pr) <sub>3</sub>	75	90:10
5	Ti(O <sup><i>i</i></sup> Pr) <sub>4</sub>	50	90:10
6	Me <sub>2</sub> SiCl <sub>2</sub>	50	85:15
7	Me <sub>3</sub> SiCl	60	83:17

Zinc dichloride (entry 1) proved to afford the best results both with respect to yield and diastereoselectivity. The lower yield obtained with the use of tetrakisopropylorthotitanate (entry 5) was reasoned to be caused by the crotyl ester being transesterified by titanium(IV) catalysis. It is worthwhile also noting the advantage that the metal salts provide over the silyl ketene acetals (entries 6 and 7) with increased yields and diastereoselectivity observed.

### 1.5.3 Quaternary Centres in the Ireland-Claisen Rearrangement

Kazmaier *et al.* extended their research into the formation of  $\alpha$ -amino acids using the chelate version of the Ireland-Claisen rearrangement by investigating the formation of quaternary centres.

There are two potential sites for formation of a new quaternary centre in Kazmaier's chelate rearrangement protocol; at the  $\alpha$ -carbon (Table 4), and the  $\beta$ -carbon (Table 5).

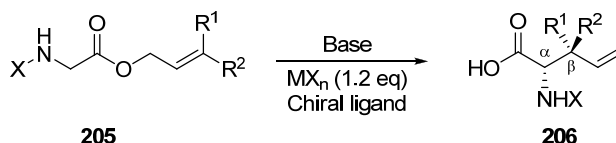
**Table 4 – Synthesis of  $\alpha$ -quaternary carbon centers**

**203**  **204**

Entry	X	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Yield (%)	de (%)
1	Cbz	H	H	Me	90	90
2	TFA	Me	H	Me	84	96
3	Cbz	Et	Me	H	87	N/A
4	Cbz	<i>i</i> Pr	Me	H	39	N/A
5	Boc	<i>i</i> Bu	Me	H	62	N/A
6	Cbz	CH <sub>2</sub> Ph	Me	H	63	N/A
7	TFA	Ph	H	Me	94	95

$\alpha$ -Alkylated amino acids, containing quaternary centres are an interesting class of compounds, chiefly because of their activity as enzyme inhibitors.<sup>170</sup> Whilst Steglich's oxazole-based rearrangement is suitable for the synthesis of  $\alpha$ -alkylated amino acids, Kazmaier furthered the chelate-based rearrangement with an investigation into the synthesis of these sterically demanding compounds (Table 4).<sup>163, 167</sup> A range of *N*-protected amino acids **203** were subjected to Kazmaier's conditions, and little dependence on the protecting group was found. With the exception of the phenylglycine derivative (entry 7) the yields are lower than found for the original, unsubstituted glycine (entry 1). These results start to show some of the additional substitution that can be applied to the substrates, providing a vast array of potential substitution patterns.

In particular, di-substitution of the olefin provides access to amino acids containing  $\beta$ -quaternary centres; themselves useful building blocks in the synthesis of natural products such as bottromycin A.<sup>171</sup> Kazmaier has shown that utilising such olefin substitution does indeed provide  $\beta$ -quaternary centres in moderate to good yield (Table 5).<sup>168</sup>

Table 5 - Synthesis of  $\beta$ -quaternary carbon centres

Entry	X	R <sup>1</sup>	R <sup>2</sup>	MX <sub>n</sub>	Yield <sup>[a]</sup> (%)	ds <sup>[b]</sup> (%)	ee <sup>[b]</sup> (%)
1 <sup>[c]</sup>	Cbz	Me	Me	ZnCl <sub>2</sub>	81	N/A	N/A
2 <sup>[c]</sup>	Boc	-(CH <sub>2</sub> ) <sub>4</sub> -	Me	ZnCl <sub>2</sub>	64	N/A	N/A
3 <sup>[d]</sup>	TFA	Naphthyl	Me	Al(O <sup><i>i</i></sup> Pr) <sub>3</sub>	70	50	N/A
4 <sup>[d],[e]</sup>	TFA	(CH <sub>2</sub> ) <sub>2</sub> -CH=C(CH <sub>3</sub> ) <sub>2</sub>	Me	Al(O <sup><i>i</i></sup> Pr) <sub>3</sub>	51	98	85
5 <sup>[d],[e]</sup>	TFA	Cyclohexyl	Me	Al(O <sup><i>i</i></sup> Pr) <sub>3</sub>	30	90	86
6 <sup>[d],[e]</sup>	TFA	-(CH <sub>2</sub> ) <sub>5</sub> -	Me	Al(O <sup><i>i</i></sup> Pr) <sub>3</sub>	70	N/A	86

<sup>[a]</sup> after methylation    <sup>[b]</sup> Determined by GC    <sup>[c]</sup> 3.5 eq LDA    <sup>[d]</sup> 5.5 eq LHMDs    <sup>[e]</sup> 2.5 eq Quinine

It has also been shown that by coordinating chiral ligands to the metal centre of the intermediate complex it is possible to develop an asymmetric chelate enolate Claisen rearrangement (entries 4-6).<sup>169</sup> Both acyclic and cyclic substrates were amenable to the rearrangement with the six-membered ring affording a good ee when a chiral ligand was used (entry 6). Excellent diastereoselectivity was seen with the geranyl ester (entry 4), again with good enantioselectivity when quinine was present. The addition of the quinine results in the formation of a chiral chelated enolate which subsequently undergoes rearrangement imparting enantioselectivity in the product.

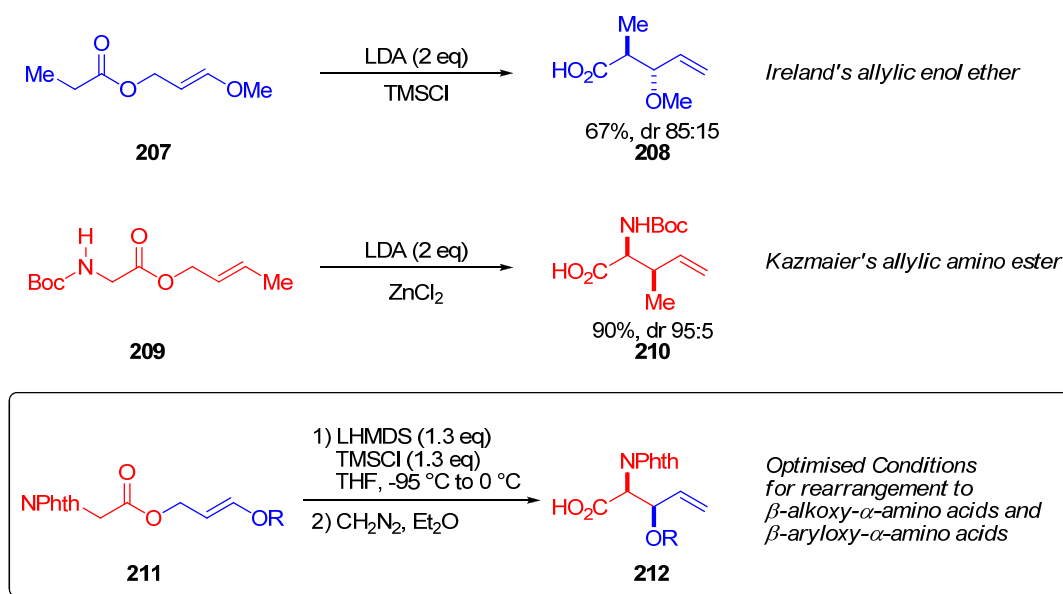
These results show that by changing the substitution pattern of the substrate both  $\alpha$ - and  $\beta$ -quaternary centres can be synthesised using the Ireland-Claisen rearrangement and that good diastereoselectivities and enantioselectivities are attainable.

## 2. $\alpha$ -QUATERNARY CENTRES IN $\beta$ -HYDROXY- $\alpha$ -AMINO ACIDS

### 2.1 Background

The use of the Ireland-Claisen rearrangement as the key reaction in the synthesis of  $\beta$ -alkoxy- and aryloxy- $\alpha$ -amino acids has previously been shown by this research group.<sup>172-173</sup> The rearrangement provides control of the stereocentres formed *via* the geometries of the enolate and alkene, and the tolerance of a large number of functionalities allows the final product to be used as a building block in the synthesis of natural products and other complex structures.<sup>174</sup>

The choice of substrate class was derived from two pertinent rearrangements. The first was Ireland's allylic enol ether **207** which rearranged to give an *anti*- $\beta$ -alkoxy acid **208**.<sup>153</sup> The second rearrangement was reported by Kazmaier, where he demonstrated the rearrangement of allylic amino ester **209** to the *syn*-allylic amino ester **210** *via* a chelated zinc enolate.<sup>166</sup> Subsequent optimisation followed to secure a reliable and efficient route to a range of  $\beta$ -alkoxy- and  $\beta$ -aryloxy- $\alpha$ -amino acids **212**.

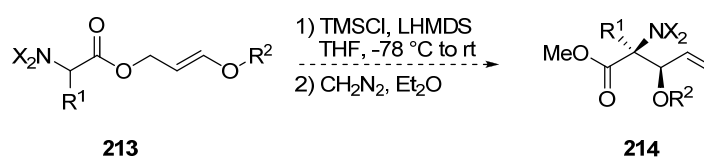


Scheme 50 - New Ireland-Claisen route to  $\beta$ -alkoxy- and  $\beta$ -aryloxy- $\alpha$ -amino acids

It is envisioned that this method can be extended to allow the synthesis of sterically congested  $\alpha$ -quaternary carbon centres in  $\beta$ -hydroxy- $\alpha$ -amino acids **214** (Scheme 51).

This is appealing as the  $\alpha$ -substituted  $\beta$ -hydroxy- $\alpha$ -amino acid moieties seen in a number of important natural products, such as lactacystin and salinosporamide A, could be synthesised from simple substrates using this method.

A range of substrates will be synthesised for an investigation into the effect of substituents in the  $\alpha$ -position. Furthermore the effect of nitrogen protecting group will also be investigated.



**Scheme 51 - Ireland-Claisen synthesis of  $\alpha$ -quaternary centres in  $\beta$ -hydroxy- $\alpha$ -amino acids**

## 2.2 Phthaloyl Protected Substrates

Based on the initial work towards the synthesis of  $\beta$ -hydroxy- $\alpha$ -amino acids the decision to use a phthaloyl protecting group was a natural one.<sup>172</sup> It has been shown to be effective under the established conditions, and protects both available sites on the nitrogen simultaneously. With an electron withdrawing nature and the ability for chelation between the carbonyls and the lithium enolate it should aid in the selective silyl ketene acetal formation.

### 2.2.1 Retrosynthetic Analysis

With a clearly defined aim, and a suitable substrate chosen, it was necessary to establish a suitable route to prepare the substrate. It is therefore necessary to apply a retrosynthesis back to an easily obtainable precursor and then employ the forward synthesis to obtain a suitable quantity of the substrate, and subsequently orchestrate the rearrangement to identify the optimum conditions.

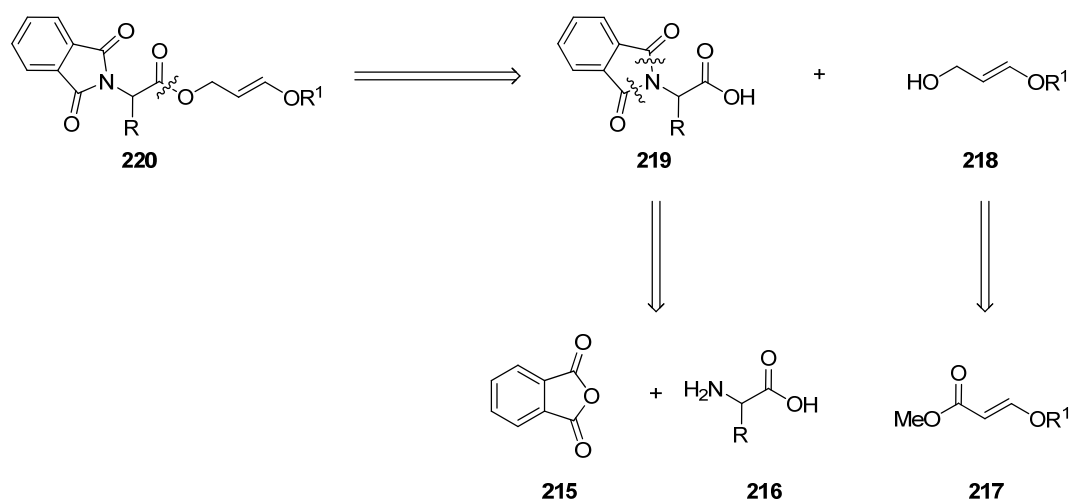
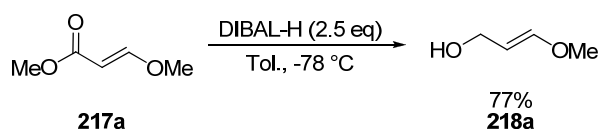


Figure 16 - Retrosynthetic analysis of phthaloyl protected substrate

The retrosynthesis takes us to three readily available commercial compounds, where variation of the R-substituent is achieved through the use of a variety of  $\alpha$ -amino acids. Enol ether **218** is prepared *via* reduction of the vinylogous carbonate **217**, which will be subjected to carbodiimide coupling conditions with the phthaloyl protected amino acid to provide a short route into the desired substrate **220**.

### 2.2.2 Forward Synthesis

Enol ether **218a** was synthesised by the DIBAL-H reduction of commercially available methyl *trans*-methoxyacrylate. The methyl ether was chosen due to its simplicity, and the commercial availability of the starting vinylogous carbonate. There have been many papers published reporting this synthesis, however, they all state the sensitivity of the product, noting that it was difficult to store, hard to purify, and that it was normally used in its crude form.<sup>153, 175-177</sup>



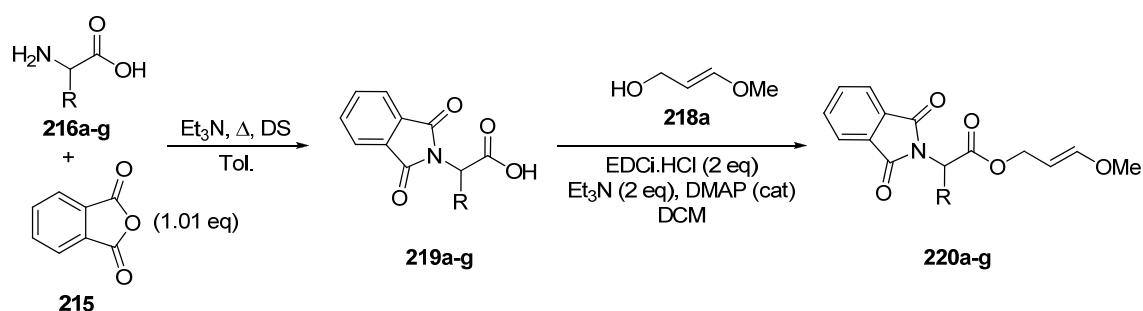
Scheme 52 - Reduction of methyl *trans*-methoxyacrylate



Numerous methods of quenching the reaction were detailed across the publications; however, quenching at 0 °C with an ethyl acetate and Rochelle's salt solution afforded us the highest yield.

With the enol ether in hand it was necessary to synthesise a range of protected  $\alpha$ -amino acids **219a-g**. Commercially available  $\alpha$ -amino acids **216a-g** were protected by refluxing in toluene with phthalic anhydride **215** under Dean Stark conditions. It was found that reducing the equivalents of phthalic anhydride used by Jurczak *et al.* to 1.01 helped increase the purity and yield of the resultant products.<sup>178</sup> Attempts to protect serine with phthalimide were, however unsuccessful and resulted in multiple spots by TLC, from which the desired product was unable to be isolated.

**Table 6 - Synthesis of *N*-phthaloyl protected Ireland-Claisen substrates**



Entry	Substrate	R	Yield of 219 (%)	Yield of 220 (%)
1	<b>216a</b>	H	N/A <sup>[a]</sup>	74
2	<b>216b</b>	Me	79	82
3	<b>216c</b>	Et	77	100
4	<b>216d</b>	<i>i</i> Pr	94	94
5	<b>216e</b>	<i>n</i> Pr	81	70
6	<b>216f</b>	<i>i</i> Bu	78	75
7	<b>216g</b>	CH <sub>2</sub> OH	0	N/A

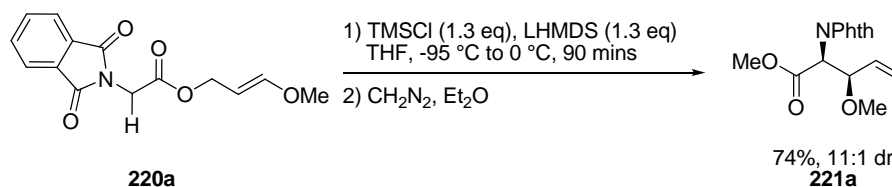
<sup>[a]</sup> Commercially available

Carbodiimide promoted coupling of protected  $\alpha$ -amino acids **219** with methoxy enol ether **218a** lead to the desired substrates **220** in good to excellent yields. Optimised conditions for the coupling reaction proved to be a 2:1 ratio of *N*-phthaloyl  $\alpha$ -amino acid to methoxy enol ether, with 2 equivalents of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDCi.HCl) and triethylamine and a catalytic quantity ( $\approx 10$

mol%) of DMAP. Increase in the amount of *N*-phthaloyl  $\alpha$ -amino acid used led to a small quantity of its anhydride formed which was inseparable from the desired product **220**.

### 2.2.3 Initial Rearrangement Attempts

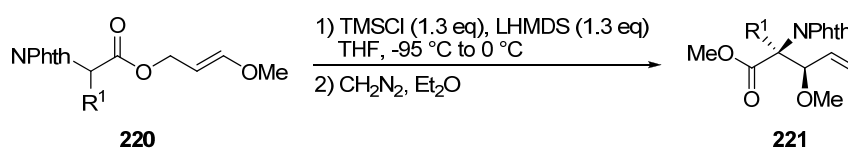
With the substrates in hand, the Ireland-Claisen rearrangement was attempted. It was envisaged that the conditions employed for the Ireland-Claisen rearrangement of glycine based systems (Scheme 53) would have the same effect with these  $\alpha$ -substituted derivatives.



**Scheme 53 - Rearrangement conditions for non-quaternary centres**

This proved to be the case for the alanine derived substrate **220b** only. It rearranged in 71% yield with a diastereoselectivity of 24:1. This promising result showed that increasing the size of the group at the  $\alpha$ -position (from a proton to a methyl group) had a dramatic effect on the selectivity of the reaction (Table 7 entry 1 and 2).

**Table 7 - Initial rearrangement attempts**



Entry	Substrate	R	Conversion (%) <sup>[c]</sup>	dr ( <i>syn:anti</i> )
1 <sup>[a]</sup>	<b>220a</b>	H	100 (74)	11:1
2 <sup>[a]</sup>	<b>220b</b>	Me	100 (71)	24:1
3 <sup>[b]</sup>	<b>220c</b>	Et	44	2.4:1
4 <sup>[b]</sup>	<b>220d</b>	<i>i</i> Pr	0	N/A
5 <sup>[b]</sup>	<b>220e</b>	<i>n</i> Pr	40	1.1:1
6 <sup>[b]</sup>	<b>220f</b>	<i>t</i> Bu	0	N/A

<sup>[a]</sup> 90 mins <sup>[b]</sup> 18 hours <sup>[c]</sup> Product against starting material. Isolated yields in parenthesis.

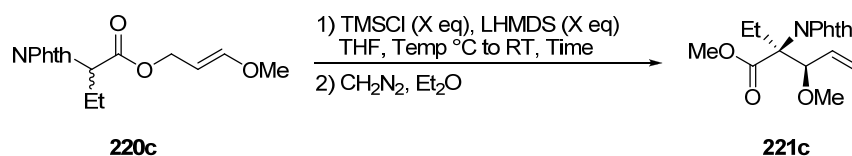
On increasing the steric bulk around the  $\alpha$ -position problems started to arise. Rearrangement of linear 2-aminobutyric derivative **220c** (entry 3) and norvaline derivative **220e** (entry 5) showed only moderate conversion, even after extended reaction times of 18 hours. In addition to the disappointing conversions, the diastereoselectivity fell when compared to the glycine (**220a**, entry 1) and alanine (**220b**, entry 2) rearrangements, with 2.4:1 and 1.1:1 seen respectively. On attempting rearrangement of branched substrates no product was seen, with starting material returned for both valine derivative **220d** (entry 4) and leucine derivative **220f** (entry 6). It can be proposed that the branched substrates sterically crowd the  $\alpha$ -position such that either deprotonation, or rearrangement cannot take place. The linear nature of **220c** and **220e** are such that whilst affecting the outcome of the reaction, they do not prevent it from occurring.

These results, whilst not showing the same success as seen previously still has the potential to achieve a successful rearrangement. A series of optimisations are necessary to develop the route further.

## 2.2.4 Rearrangement Optimisation

### 2.2.4.1 Optimisation for *N*-Phthaloyl (*E*)-3-methoxyallyl 2-aminobutanoate

Methoxyallyl 2-aminobutyric acid derived **220c** showed potential for optimisation when rearranged under the initial conditions, with a 44% conversion and diastereoselectivity of 2.4:1 observed (Table 8, entry 1). Extending the reaction time led to a slight increase in conversion (entry 2), as did raising the initiation temperature to -78 °C (entry 4). The largest gains were, however, found by increasing the equivalents of LHMDs and TMSCl from 1.3 to 2 (entries 2 and 4 compared to entries 3 and 5). High conversions were observed, with a diastereomeric ratio of 2.7:1 when conducted at -78 °C. After purification this resulted in a yield of 20%. A small amount of the parent amino acid **219c** was also observed, isolated as its methyl ester, as an additional 2% of the mass returned. The additional mass lost can be postulated to be caused by degradation of the enolate prior to silylation.

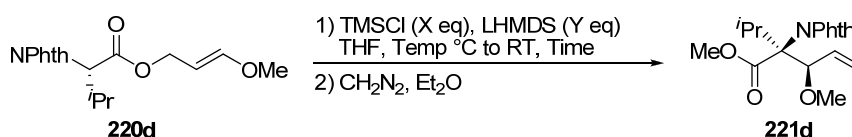
Table 8 - Optimisation for *N*-phthaloyl 2-aminobutyric acid allyl ester

Entry	Temp	TMSCl (eq)	LHMDs (eq)	Time (hrs)	Conversion (%) <sup>[a]</sup>	dr (syn:anti)
1	-95 °C	1.3	1.3	3	44	2.4:1
2	-95 °C	1.3	1.3 <sup>[b]</sup>	18	56	2.3:1
3	-95 °C	2	2	18	96 (19)	2.4:1
4	-78 °C	1.3	1.3	18	69	2.4:1
5	-78 °C	2	2	18	95 (20)	2.7:1

<sup>[a]</sup> Product against starting material. Isolated yields in parenthesis. <sup>[b]</sup> LHMDs added by hand

#### 2.2.4.2 Optimisation for *N*-Phthaloyl (*E*)-3-methoxyallyl 2-amino-3-methylbutanoate

After the initial rearrangement attempt, an optimisation study was undertaken to improve rearrangement of the valine derived substrate **220d** (Table 9).

Table 9 - Optimisation for *N*-phthaloyl valine allyl ester

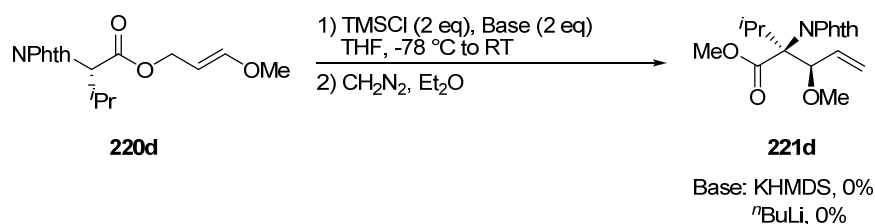
Entry	Temp	TMSCl (eq)	LHMDs (eq)	Time (hrs)	Conversion (%) <sup>[a]</sup>
1	-95 °C	1.3	1.3	3	0
2	-95 °C	2	2	3	0
3	-95 °C	3	3	3	0
4	-95 °C then RT	1.3	1.3 then 1	18	50 (11)
5	-78 °C	1.3	1.3	6	15
6	0 °C	1.3	1.3	6	18
7	0 °C	4	4	72	100 (12)

<sup>[a]</sup> Conversion stated as product against starting material. Isolated yields in parenthesis.

Increasing the amount of base and TMSCl used, to both 2, and 3 equivalents, had no bearing on the outcome of the reaction, with only starting material recovered. On

attempting the rearrangement at -95 °C with 1.3 eq, after 3 hours, when TLC showed no sign of reaction, a further equivalent of LHMDS was added to the reaction mixture at room temperature. This was left to stir overnight, where a conversion of 50% was seen, with an isolated yield of 11% (entry 4). The diastereoselectivity of this reaction was unable to be determined due to the lack of resolution between the diastereomers in the  $^1\text{H}$  NMR. Further rearrangement attempts were made at -78 °C and 0 °C, and whilst a yield of 12% was seen when four equivalents of LHMDS and TMSCl were used, there was an additional 27% mass of the parent amino acid (isolated as the methyl ester), present as an inseparable mixture.

This investigation into the rearrangement of  $\alpha$ -substituted substrates has, so far, only used LHMDS. Since a key element in all Ireland-Claisen rearrangements is the base used a short study was initiated to investigate further.

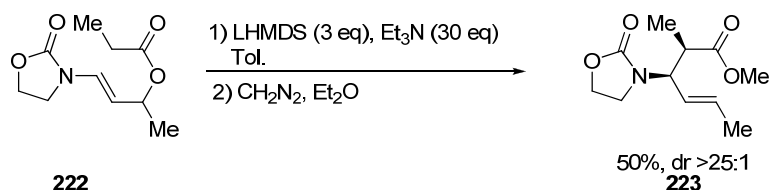


**Scheme 54 - Effect of base on rearrangement of *N*-phthaloyl valine allyl ester**

The use of KHMDS saw starting material returned, with only a trace amount of product seen after several days of stirring.  $n\text{BuLi}$  meanwhile returned only starting material after stirring for 18 hours, without any sign of product whatsoever (Scheme 54). These observations bear some resemblance to the optimisation study previously conducted within the group, on the phthaloyl glycine substrate **220a**. In those studies, it was found that switching from LHMDS to NaHMDS or KHMDS resulted in a significant drop in both yields and diastereoselectivity. Furthermore, it was discovered that use of non-ethereal solvents such as toluene led to an intractable mixture of products.<sup>179</sup>

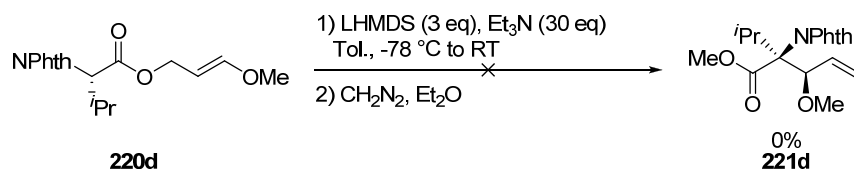
During the course of these studies, a publication by Collum *et al.* detailed LHMDS-mediated enolization, including the influence of triethylamine on the *E/Z* selectivity.<sup>180</sup> The conditions detailed in his article have been put to good use in the synthesis of  $\beta^{2,3}$ -

amino acids within our group, where the standard conditions were failing to provide adequate results (Scheme 55).<sup>181</sup>



Scheme 55 - Collum's enolization conditions

Unfortunately, after attempting these conditions in our rearrangement the complex NMR that resulted after work up showed no sign of the desired product, whilst significant quantities of starting material could be discerned (Scheme 56).

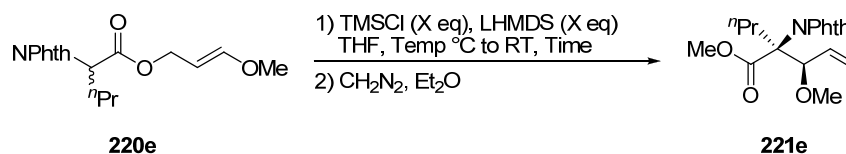


Scheme 56 - Attempted Collum rearrangement of *N*-phthaloyl valine allyl ester

Despite many failed rearrangement attempts, we have progressed from a rearrangement protocol which saw no sign of any product, and have been able to optimise these conditions to synthesise the desired  $\alpha$ -quaternary  $\beta$ -hydroxy- $\alpha$ -amino acid in 11% yield. However, it appears that the increase in steric bulk is preventing a successful reaction from occurring.

#### 2.2.4.3 Optimisation for *N*-Phthaloyl (*E*)-3-methoxyallyl 2-aminopentanoate

Norvaline derivative **220e** showed some promise for optimisation, with initial conditions producing a conversion of 40% and an approximate diastereoselectivity of 1.1:1 (Table 10, entry 1). Prolonging the reaction time to 72 hours doubled the conversion, with a small increase in diastereoselectivity (entry 2). A subsequent increase in the equivalents of LHMDS and TMSCl further increased the conversion, and affords a dr almost double that first seen (entry 3). Increasing the temperature to  $-78^\circ\text{C}$  led to an improvement in the conversion and isolated yield when compared to the comparative rearrangements at  $-95^\circ\text{C}$  (entries 5 and 6 against entry 3).

Table 10 - Optimisation for *N*-phthaloyl norvaline allyl ester

Entry	Temp	TMSCl (eq)	LHMDs (eq)	Time (hrs)	Conversion (%) <sup>[a]</sup>	dr (syn:anti)
1	-95 °C	1.3	1.3	3	40	1.1:1
2	-95 °C	1.3	1.3 <sup>[b]</sup>	72	80	1.4:1
3	-95 °C	2	2 <sup>[b]</sup>	72	95 (23)	2:1
4	-78 °C	1.3	1.3	72	95	1.9:1
5	-78 °C	2	2	72	100 (41)	3:1
6	-78 °C	2	2 <sup>[b]</sup>	72	100 (45)	2:1
7	-78 °C	3	3	72	100	1.9:1

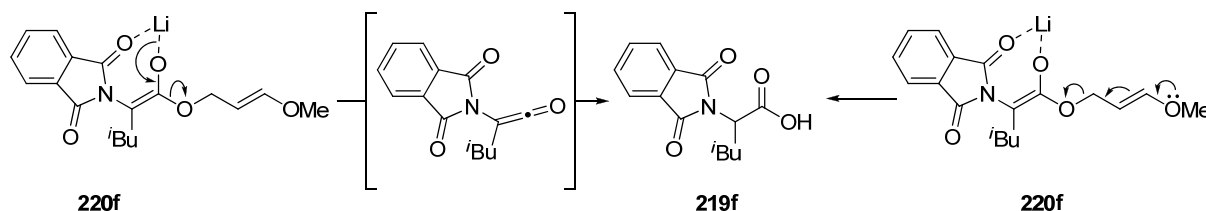
<sup>[a]</sup> Conversion stated as product against starting material. Isolated yields in parenthesis. <sup>[b]</sup> LHMDs added via syringe pump at a rate of 3mL/min

On workup and subsequent purification it becomes apparent that a side product is present. Identified as the parent amino acid (isolated as the methyl ester PhthN-Nva-OMe) it is found to have an  $R_f$  highly similar to the desired product **221e**, which made purification difficult. Unfortunately this side product was observed in all rearrangement attempts. 19% of PhthN-Nva-OMe was recovered from the rearrangement at -95 °C (entry 3), along with 23% of the desired product. On increasing the temperature, and adding LHMDs dropwise by hand, 41% of product was obtained, along with 24% of PhthN-Nva-OMe (entry 5). Due to the lack of resolved peaks in the  $^1\text{H}$  NMR it was not possible to obtain an accurate diastereomeric ratio from the crude reaction mixture, nonetheless, the two diastereomers were separable by column chromatography, whereby a ratio of 3:1 was obtained. When a syringe pump was used for the addition, with an addition rate of 3mL/min, 45% of rearranged product was obtained, with a much reduced 11% of PhthN-Nva-OMe (entry 6). This time it was possible to obtain a diastereomeric ratio of 2:1, from the crude  $^1\text{H}$  NMR.

#### 2.2.4.4 Optimisation for *N*-Phthaloyl (*E*)-3-methoxyallyl 2-amino-4-methylpentanoate

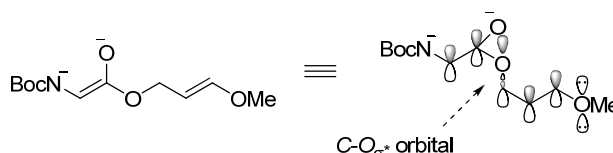
All rearrangement attempts of leucine derivative **220f** failed to show any sign of desired product. However, along with unreacted starting material, significant quantities of the

parent amino acid **219f** were recovered (isolated as the methyl ester after treatment with diazomethane). These results were seen when using either 2, or 3 equivalents of LHMDS at -78 °C, and with reaction times of both 18 and 48 hours.



**Scheme 57 - Postulated mechanisms for decomposition to parent amino acid**

Whilst there is no conclusive evidence for the mechanism for the formation of the parent amino acid, two plausible mechanisms are shown in Scheme 57. Such decomposition was originally seen when a simple *N*-Boc glycine derivative was being used, under Kazmaier's chelate enolization conditions (LHMDS and  $\text{ZnCl}_2$ ). The rationale in the chelate example was the dianionic nature of the intermediate enolate (Figure 17). It was argued that the  $\text{C}-\text{O}_{\sigma^*}$  orbital is overlapped by two highly electron rich  $\pi$ -systems, which allow a significant level of electron density to be donated into the  $\sigma^*$  orbital.<sup>173</sup>



**Figure 17 - Possible enolate instability under chelate enolization**

In our scenario however, the additional substitution present may provide enough electron density to cleave this  $\text{C}-\text{O}$  single bond. Furthermore, it is likely to help stabilise the ketene intermediate. Presumably this decomposition route occurs rapidly, such that silylation is unable to take place and prevent it.

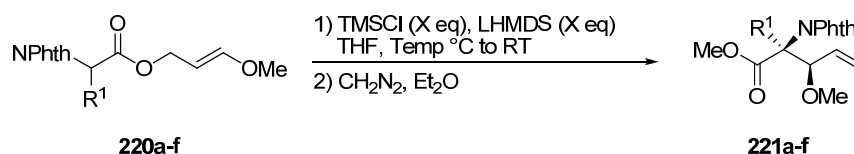
### 2.2.5 Optimal Rearrangements

During the course of the investigation into the rearrangement of *N*-phthaloyl- $\alpha$ -substituted-amino acids we have found that as the substituent size is increased the



rearrangement becomes far less facile, up to leucine, whereby no rearrangement is seen, but rather a complete decomposition of the substrate to the parent amino acid. It has been necessary to acquire different conditions for each amino acid, to obtain optimal results (Table 11).

**Table 11 - Optimal rearrangement results**



Entry	Substrate	R	Temp	TMSCl (eq)	LHMDS (eq)	Yield (%) <sup>[a]</sup>	dr (syn:anti)
1	<b>220a</b>	H	-95 °C	1.3	1.3	74 (100)	11:1
2	<b>220b</b>	Me	-95 °C	1.3	1.3	71 (100)	24:1
3	<b>220c</b>	Et	-78 °C	2	2	20 (95)	2.7:1
4	<b>220d</b>	<i>i</i> Pr	-95 °C	1.3	1.3 & 1	11 (50)	N/A
5	<b>220e</b>	<i>n</i> Pr	-78 °C	2	2	45 (100)	2:1
6	<b>220f</b>	<i>i</i> Bu	-78 °C	2	2	0	N/A

<sup>[a]</sup> Conversions in parenthesis, stated as product against starting material.

There are two potential reasons for the poor results achieved with the larger groups. The first of these is the inability of the base to deprotonate the  $\alpha$ -proton and hence form the silyl ketene acetal. The second is the inability for the rearrangement to take place once the silyl ketene acetal has been formed. The reasoning behind both these possibilities lie with steric crowding; it can be seen that the branched chains (entries 4 and 6) offer poor rearrangements, whilst improved results are obtained with the linear substrates (entries 2, 3 and 5), which would present less steric hindrance around the  $\alpha$ -position, hence improving deprotonation, or the ability for the allyl group to approach in order to undergo rearrangement. A 3D representation of the silyl ketene acetal for substrate **220d** shows the *iso*-propyl substituent crowding the key reaction site (Figure 18).

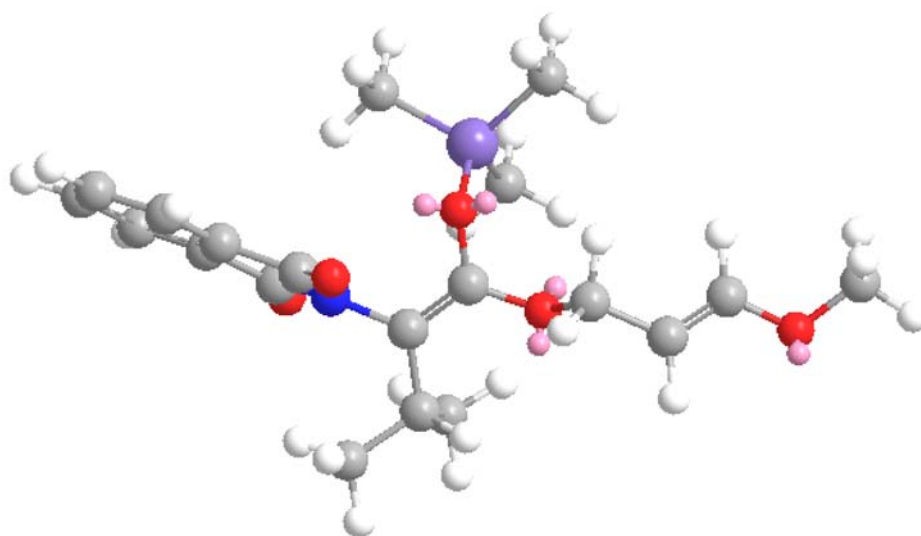
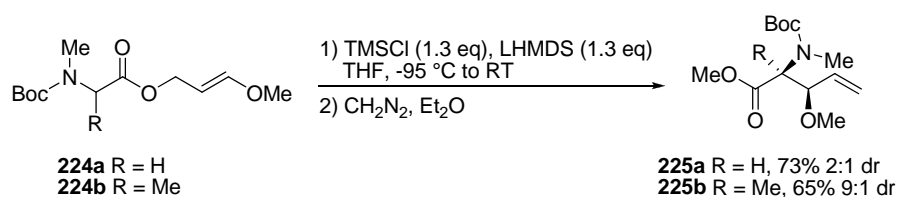


Figure 18 - 3D representation of the silyl ketene acetal for *N*-phthaloyl valine allyl ester

### 2.3 Boc-*N*-Me Protected Substrates

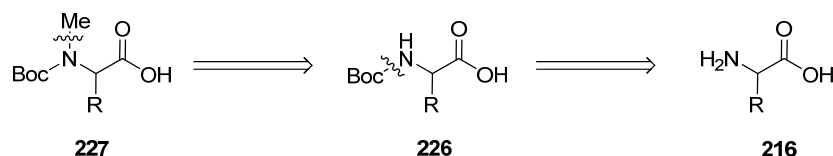
It is known, both from within the group and from other Ireland-Claisen rearrangements that the nitrogen protecting group can have a large bearing on the success of the rearrangement. As part of an investigation into derivatives of glycine-based substrates it has been demonstrated that Boc-sarcosine-methoxyallyl ester **224a** undergoes rearrangement in 73% yield with a diastereomeric ratio of 2:1 (Scheme 58).<sup>173</sup> In the course of this previous study Boc-*N*-Me-alanine derivative **224b** had also been found to rearrange satisfactorily, in 65% yield and a diastereomeric ratio of 9:1.<sup>182</sup> Consequently we wanted to attempt the rearrangement with other  $\alpha$ -substituted amino acids.



Scheme 58 - Rearrangement of Boc-*N*-Me-glycine allyl esters

#### 2.3.1 Retrosynthetic Analysis

With the new series of substrates identified a new route was needed to prepare them. Whilst the synthesis of the allylic enol ether remains the same, protection of the amino acid needs to be established.

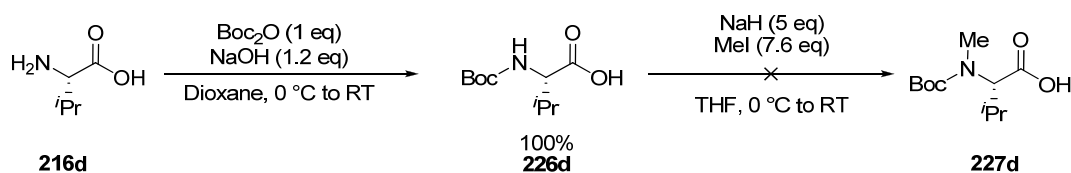


**Figure 19 - Retrosynthetic Analysis of Boc- *N*-Me Protected Substrate**

The forward route requires the protection to take place in two steps, namely Boc protection of the amino acids, followed by *N*-methylation.

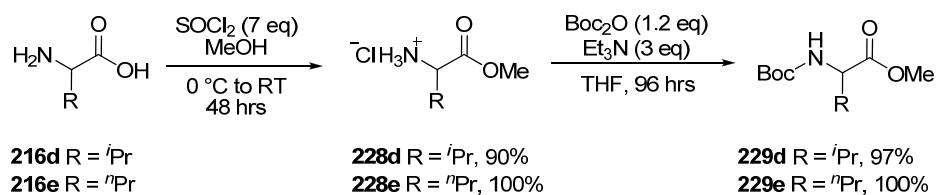
### 2.3.2 Forward Synthesis

With the proposed route in place the first step – Boc protection – took place in quantitative yield. *N*-Boc valine **226d** was carried forward in its crude form to the alkylation using methyl iodide and sodium hydride, in DMF. However, despite following a literature procedure, the result was an intractable mixture of starting material and impurities (Scheme 59).<sup>183</sup>



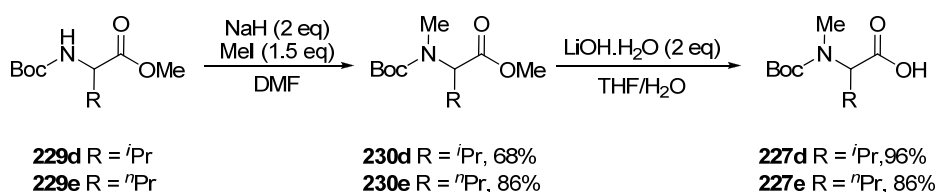
**Scheme 59 - Initial synthetic attempt**

It was reasoned that the methylation might proceed more successfully if the carboxylic acid was protected as the methyl ester. A new synthesis was therefore designed (Scheme 60 and Scheme 61). Initial esterification proceeded in an excellent yield of 90%. A variety of conditions were investigated for the subsequent Boc protection. Using sodium hydroxide as the base resulted in hydrolysis of the methyl ester, so triethylamine was used instead. By performing the reactions in water, lower yields were seen, in part due to partial water solubility of the product, requiring multiple extractions. Performing the reaction in THF presented a simple workup; concentration *in vacuo*, and then purification by flash chromatography. The single disadvantage was long reaction times of 96 hours to attain high yields of the Boc protected amino esters **229d** and **229e**.

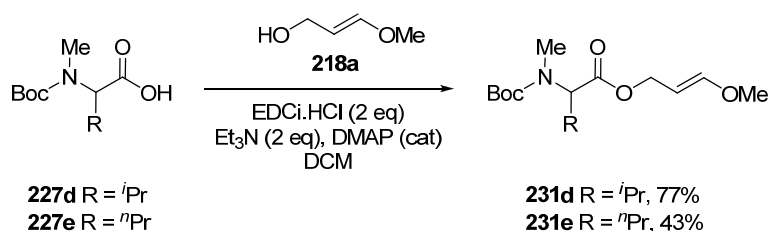


Scheme 60 - Revised synthetic route

The methylation that followed occurred in good yield when using sodium hydride and methyl iodide in DMF. This route avoided the large amounts of both sodium hydride and methyl iodide that were used in the previous unsuccessful attempt. Ensuing hydrolysis with lithium hydroxide afforded the desired Boc-*N*-Me-valine **227d** and Boc-*N*-Me-norvaline **227e** in 96% and 86% yields respectively.

Scheme 61 - Synthesis of *N*-Boc *N*-Me protected amino acids

The final stage of the synthesis was carbodiimide promoted coupling of protected amino acids **227d-e** with allylic enol ether **218a**, which proceeded in good yield for valine derived substrate **231d** (Scheme 62). It did however give a disappointing yield of *N*-Boc-*N*-Me-norvaline allyl ester **231e**. This was however, in part, due to partial decomposition whilst undergoing purification by flash chromatography.

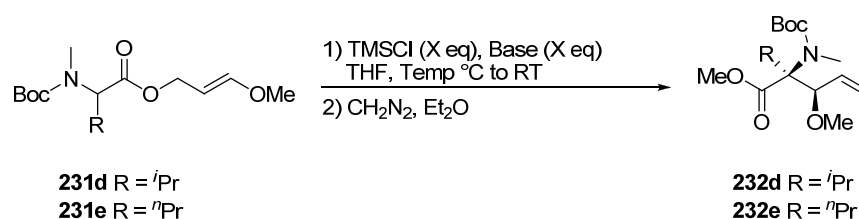


Scheme 62 – Completion of substrate synthesis

### 2.3.3 Rearrangement Attempts

Initial efforts concentrated on Boc-*N*-Me-valine allyl ester **111a**. As was the case with *N*-phthaloyl valine, the original conditions resulted only in starting material being recovered.

**Table 12 - Optimisation of *N,N*-Boc,Me valine allyl ester**



Entry	Substrate	Temp	TMSCl (eq)	LHMDS (eq)	Base	Time (hrs)	Conversion (%) <sup>[a]</sup>
1	<b>231d</b>	-95 °C	1.3	1.3	LHMDS	3	0
2	<b>231d</b>	-78 °C	2	2	LHMDS	3	0
3	<b>231d</b>	0 °C	2	2	LHMDS	3	0
4	<b>231d</b>	-78 °C	2	2	KHMDS	5	0
5	<b>231e</b>	-78 °C	2	2 & 1	LHMDS	18	0

<sup>[a]</sup> Conversion stated as product against starting material. Isolated yields in parenthesis.

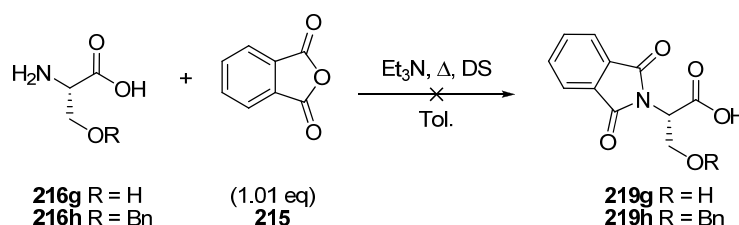
Increasing the temperature and the equivalents of base and TMSCl had no effect, and switching to the base KHMDS made no difference to the overall result (Table 12).

Since more success had been seen for the rearrangement of the *N*-phthaloyl norvaline allyl ester **220e** over the valine derivative **220d**, it was decided to attempt the rearrangement of the analogous Boc-*N*-Me-norvaline allyl ester **231e** (Table 12). However, this failed to rearrange at -78 °C with 2 equivalents of LHMDS, and even an additional equivalent of base at room temperature failed to provide any conversion.

Since this series was showing little potential it was decided to focus on other areas of chemistry which showed more signs of promise.

## 2.4 Heteroproline Derived Substrates

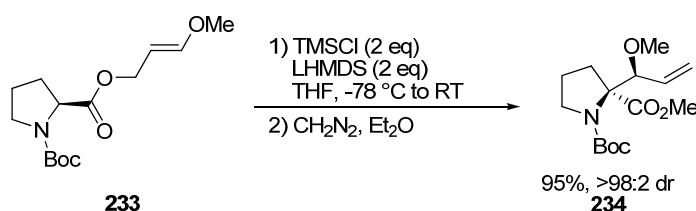
Earlier attempts to protect serine with phthalimide had been unsuccessful; however, due to its ubiquitous nature it is a highly desirable substrate where the  $\alpha$ -substituted serine that results from the rearrangement can be used as a building block for natural products.



Scheme 63 - Synthetic attempts towards *N*-phthaloyl serine

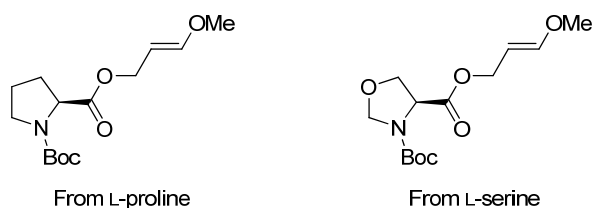
### 2.4.1 Substrate Genesis

Whilst investigating alternative methods of protecting serine we were drawn to the success seen when rearranging the proline-derived substrate **233**. Under modified rearrangement conditions – the same used when rearranging the *N*-phthaloyl protected substrates **220c** and **220e** – a highly successful rearrangement was observed (Scheme 64). A single diastereomer was recovered in a near quantitative yield.<sup>179</sup>



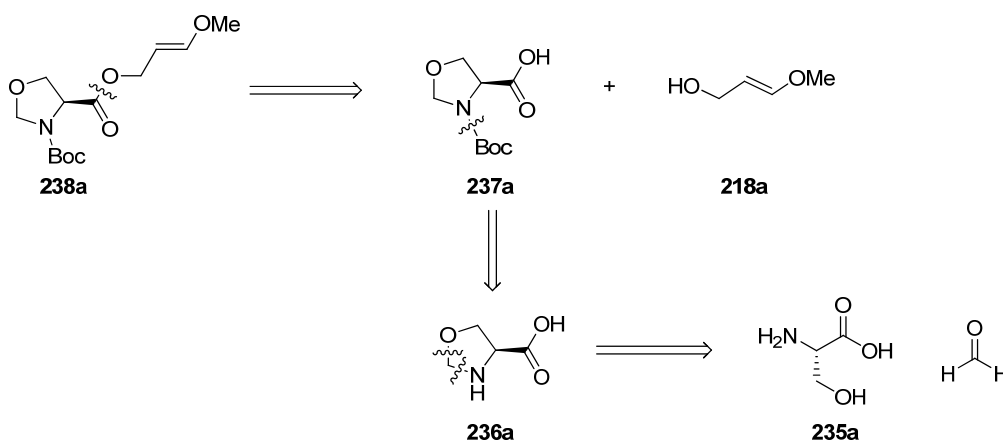
Scheme 64 - Rearrangement of *L*-proline methoxyallyl ester

This observation led us to postulate that serine could be protected with formaldehyde to form a cyclic *N,O*-acetal, such that structurally it would be very similar to proline (Figure 20). Furthermore, this has the potential to allow cysteine, and threonine to be protected in the same manner, and hence allow more structurally diverse building blocks to be created.



**Figure 20 - Protection of L-serine analogous to L-proline**

With a clear idea of the substrate required for the Ireland-Claisen rearrangement a synthetic route is needed for its synthesis. As with the retrosyntheses from the previous sections the first retrosynthetic step is disconnection at the acyl bond to provide protected amino acid **237** and enol ether **218a**. Serine **235a** can be used to synthesise the oxazolidine **236**, which, after Boc protection will afford the protected amino acid ready for coupling with **218a**.



**Scheme 65 - Retrosynthetic analysis of oxaproline substrate**

#### 2.4.2 Forward Synthesis of Heteroproline Allyl Esters

The retrosynthetic scheme (Scheme 65) can, in practice, be readily shortened. It has previously been demonstrated that *N*-Boc-4-carboxy-1,3-oxazolidine (4-oxaproline) **237a** can be synthesised in high yields, in a one-pot procedure.<sup>184</sup> Serine is dissolved in an aqueous solution of sodium hydroxide and paraformaldehyde, and left in the fridge overnight. Boc anhydride and a catalytic amount of hydroxylamine hydrochloride are subsequently added at room temperature and left to stir for three hours to furnish the desired oxaproline in excellent yield.

Table 13 - Synthesis of *N*-Boc heteroprolines

Entry	Substrate	X	R	Yield of 237 (%)
1	<b>235a</b>	O	H	93
2	<b>235b</b>	S	H	77
3	<b>235c</b>	O	Me	97

This method was also used with great success with cysteine and threonine, in addition to serine, to afford three newly protected amino acids ready for esterification (Table 13).

Carbodiimide promoted esterification occurred in moderate yield (Table 14); this can be partly explained by the sensitivity of the products. The threonine substrates were particularly sensitive, and where further purification was necessary a short pad of base-treated silica was used (see 3.3.1 Substrate Synthesis for an in-depth discussion on the synthesis of enol ethers **218** and subsequent esterification).

Table 14 - Synthesis of *N*-Boc heteroproline allyl esters

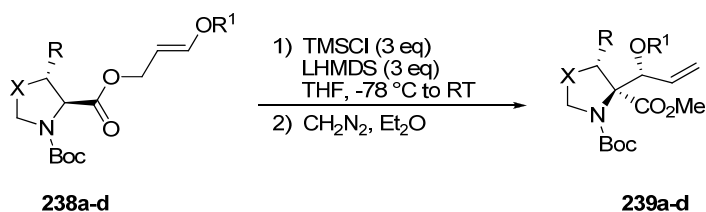
Entry	Product	X	R	R <sup>1</sup>	Yield (%)
1	<b>238a</b>	O	H	Me	67
2	<b>238b</b>	S	H	Me	63
3	<b>238c</b>	O	Me	Me	56
4	<b>238d</b>	O	Me	Et	45



### 2.4.3 Rearrangement of Heteroproline Allyl Esters

The proline allyl esters that have been previously subjected to the Ireland-Claisen rearrangement have required higher temperatures and more base than the *N*-phthaloyl glycinate to achieve complete conversion. Due to the similarity of our current substrates to these it was foreseen that similar conditions would be necessary. Initial attempts using 2 equivalents of both LHMDS and TMSCl showed promising signs of reactivity. However, after 18 hours there was still residual starting material. By increasing the number of equivalents to 3 the reaction was able to go to completion.

**Table 15 - Rearrangement of heteroproline allyl esters**



Entry	Product	X	R	R <sup>1</sup>	Yield (%)	dr ( <i>syn:anti</i> )
1	<b>239a</b>	O	H	Me	50	6:1
2	<b>239b</b>	S	H	Me	44	12:1
3	<b>239c</b>	O	Me	Me	47	>99:1
5	<b>239d</b>	O	Me	Et	70	>99:1

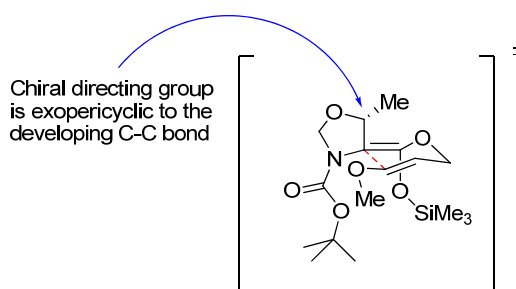
The initial findings show that whilst the yields are moderate to good, the diastereomeric ratios are very positive. Both the serine **239a** and cysteine **239b** rearrangement products show good diastereoselectivity, whilst the threonine derivatives **239c** and **239d** rearrange as single diastereomers (Table 15). For compound characterisation variable temperature (VT) NMR was necessary to ensure that the rotameric peaks were not screening any diastereomeric peaks.

Due to the use of enantiomerically pure threonine, the additional methyl group present on the oxazolidine ring creates a chiral centre. This shows that there is the potential for enantiomeric control with this reaction, with transfer of chirality controlled by this stereocentre.

### 3. SRS IN AN IRELAND-CLAISEN REARRANGEMENT

#### 3.1 Concept Development

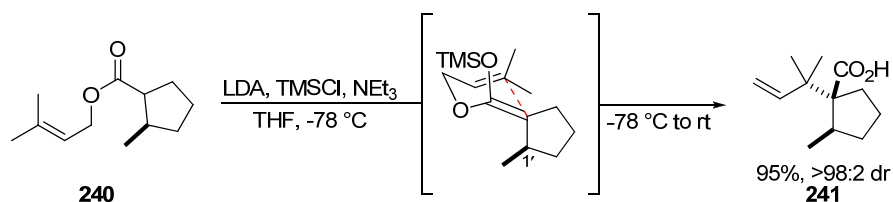
The success seen in the rearrangement of threonine allyl esters **239c** and **239d** led us to the belief that we could induce similar chirality control with serine. However, any such attempts would require – as is the case in the rearrangements of **239c** (Figure 21) – the asymmetric transfer to be outside the cyclic transition state.



**Figure 21 - The exopericyclic nature of the directing group in the heteroproline Ireland-Claisen rearrangement**

Whilst the transfer of chirality within the cyclic framework is well documented, this is not the case for the consequences of chirality sited outside such a framework.<sup>185</sup> There are scattered examples in the literature that show limited efficacy in asymmetric synthesis. For the subsequent discussion, the stereocentres will be assigned based on their relative location to the silyl ketene acetal. Carbons  $\alpha$  to the C1 carbon will be designated C1',  $\alpha$  to C5, C5' and so on.

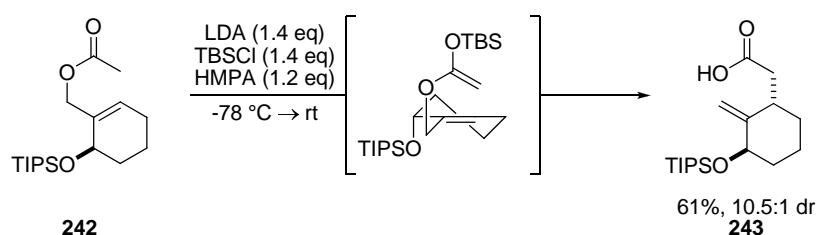
Gilbert *et al.* showed that the rearrangement of a prenyl cyclopentyl ester with a methyl substituent at C1' gave high facial selectivity (Scheme 66).<sup>186</sup> This selectivity was due to the approach of the prenyl group *anti* to the C1' methyl group in the transition state. The same diastereomer would be achieved regardless of the geometry of the silyl ketene acetal, or rearrangement through either a chair or boat transition state.



Scheme 66 - Influence of a remote stereocentre at C1'

On the use of either *E*- or *Z*-crotyl esters (rather than the prenyl ester seen in Scheme 66) the same stereoselectivity was seen at the newly created quaternary centre, however, the diastereoselectivity at C3 was low. This was presumed to be due to a lack of selectivity in the formation of the silyl ketene acetal rather than the rearrangement proceeding through a combination of chair and boat transition states.

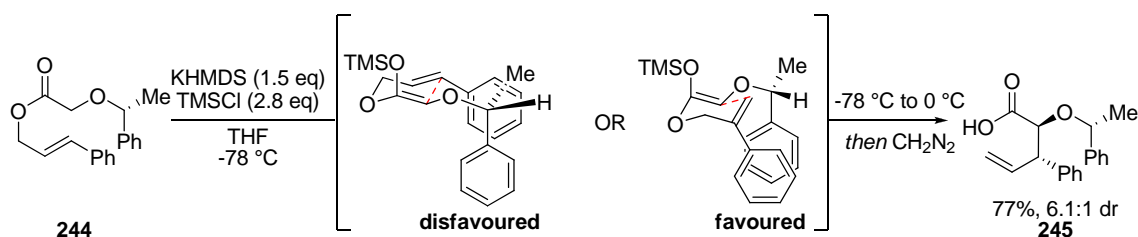
Ishizaki *et al.* used the diastereoselective Ireland-Claisen rearrangement of the C5' triisopropylsilyl ether **242** to afford the *trans*-carboxylic acid **243** with a diastereoselectivity of 10.5:1 (Scheme 67).<sup>187</sup> A range of silyl protecting groups were trialled, with the TIPS group providing the highest level of selectivity. It can be envisaged that attack of the silyl ketene acetal will be *anti* to the *O*-silyl group. In this case – whilst a chair transition state is most likely – both the chair and boat transition states would yield the same product.



Scheme 67 - Influence of a remote stereocentre at C5'

Whilst the examples above show a small selection of asymmetric induction from a chiral centre one atom removed from the cyclic transition state there are even fewer examples of selective rearrangements when the remote stereocentre is two atoms exocyclic. We have already seen one such example (see 1.5.2 Glycinates in the Ireland-Claisen Rearrangement, Scheme 48) where the use of chiral glycinates afforded asymmetric induction. Gould and Kallmerten have also reported an auxiliary-directed glycolate Ireland-Claisen rearrangement where modest selectivities were induced

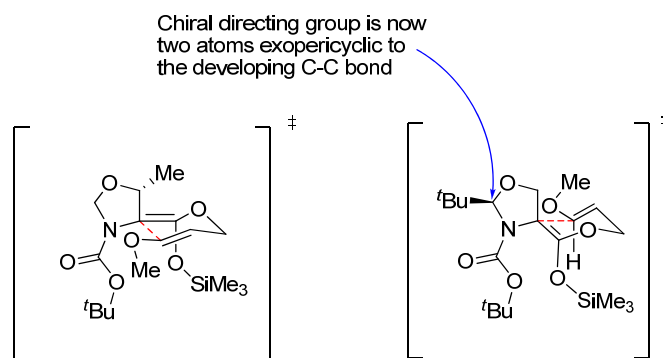
(Scheme 68).<sup>188</sup> They highlighted the synthetic utility of their method in a short synthesis of (*R*)-(-)-pantolactone.



**Scheme 68 - Glycolates as a chiral auxiliary in the Ireland-Claisen rearrangement**

Their protocol sees two alternative transition states, such that one is favoured over the other. This allows the external auxiliary to direct the facial selectivity of addition to the enolate  $\pi$ -system, allowing for a preferential outcome. In this case, the best diastereoselectivity seen was with the cinnamyl glycolates, which was rationalised due to a favourable  $\pi$ -stacking interaction.

We conceived that it would be possible to apply the principle of self-regeneration of stereocentres with an Ireland-Claisen rearrangement.



**Scheme 69 - Introduction of SRS to an Ireland-Claisen rearrangement**

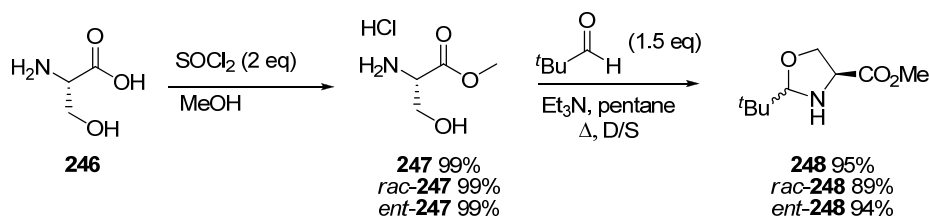
The prerequisite substrate bears a large similarity to the heteroproline compounds that were successfully rearranged previously. However, in this novel application of SRS the directing group is now two atoms exocyclic to the chair transition state, and to the developing C-C bond.

## 3.2 Reaction Development

### 3.2.1 Forward Synthesis of Chiral Oxazolidine

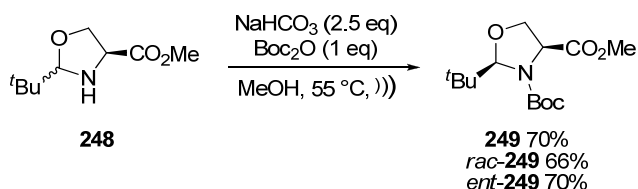
Seebach has published many papers on the use of pivalaldehyde to protect serine as an *N,O*-acetal, which will install a chiral *tert*-butyl group on the oxazolidine ring.<sup>89-90, 189-190</sup> Furthermore, Ghosez *et al.* have demonstrated that it is possible to protect the oxazolidine with a Boc group, rather than the formyl group most commonly used by Seebach.<sup>191</sup>

During the course of this investigation it was necessary to synthesise both enantiomers in addition to the racemic series. The yields for all three parallel series are shown in the relevant schemes. For a successful cyclisation of serine **246** with pivalaldehyde, it is necessary to synthesise the serine methyl ester hydrochloride salt **247**. Condensation with pivalaldehyde proceeded under Dean-Stark conditions to give the desired oxazolidine in a 64% yield after 24 hours. However, extending the reaction time by a further 24 hours afforded the methyl 2-*tert*-butyloxazolidine-4-carboxylate **248** in 95% yield, with a diastereomeric ratio of 63:37.

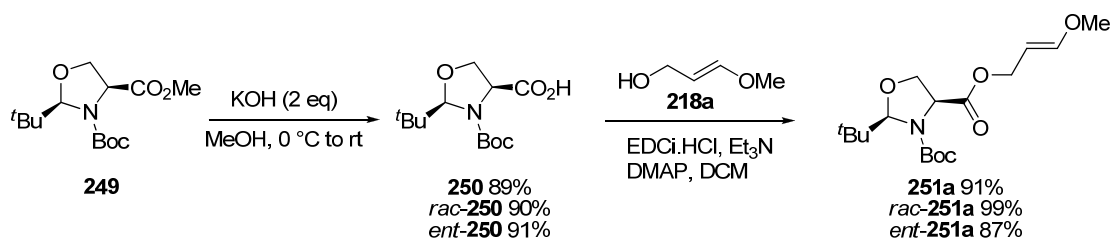


Scheme 70 - Oxazolidine Synthesis

Boc protection as reported by Ghosez *et al.* required the use of an ultrasonic bath at 55 °C. This worked well, yielding a single diastereomer of oxazolidine **249** in 70%. However, the practicalities of this method were not ideal, since it was not conducive to scale, due to the limitations in size of our sonicator. To circumnavigate this issue, a solely thermal reaction, with vigorous stirring was attempted. Again, a single diastereomer was isolated, although the yields were variable from reaction to reaction, but were always in the range of 50-70%. Despite the occasional reduction in yield, this allowed us to bring through larger quantities of starting material.

Scheme 71 - Boc protection of 2-*tert*-butyloxazolidine-4-carboxylate

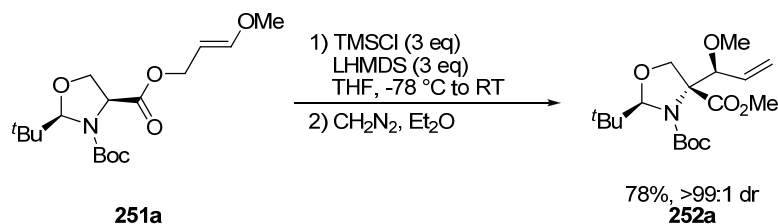
Ester hydrolysis of **249** affords the free acid in good yield, ready for carbodiimide promoted coupling to enol ether **218a**. Esterification proceeds smoothly to synthesise the desired rearrangement substrate **251a** in 91% after purification through a short pad of base treated silica.



Scheme 72 - Synthetic completion of rearrangement substrate

### 3.2.2 Rearrangement Optimisation

With the route to the desired substrate **251a** in hand, the rearrangement was investigated. The conditions used in the heteroproline rearrangements (2.4.3 Rearrangement of Heteroproline Allyl Esters) were an excellent starting point.



Scheme 73 - Initial Ireland-Claisen rearrangement attempt

The rearrangement pleasingly proceeds with a high yield, and furthermore, as a single diastereomer (Scheme 73). Polarimetry produces an  $[\alpha]_D$  of -13, showing optical activity that is comparable to similar compounds in the literature (Figure 22).<sup>192</sup>

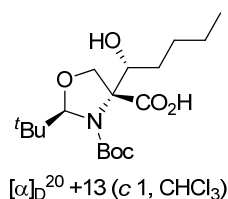


Figure 22 - Literature Precedence For Optical Activity

Before we progressed any further into developing the scope of this rearrangement, we wanted to ensure the rearrangement was fully optimised. For this purpose, a small screen of conditions was conducted.

Table 16 - Optimisation of oxazolidine rearrangement



Entry	Temp (°C)	TMSCl (eq)	LHMDS (eq)	Yield (%)	Comments
1	-95	1.3	1.3	-	SM returned
2	-95	2	2	-	Trace product
3	-78	1.3	1.3	-	Intractable mixture
4	-78	2	2	-	Intractable mixture
5	-78	3	3	78	>99:1 dr

The findings from this optimisation screen show that our initial conditions (Table 16, entry 5) show complete consumption of starting material, with an isolated yield of 78%. On reducing the number of equivalents of TMSCl and LHMDS there is an increase in the quantity of residual starting material present. This forms an intractable mixture with the desired product, and isn't amenable to separation by flash chromatography. On lowering the temperature to -95 °C the reaction is stopped, and only trace amounts of product can be seen, whilst large quantities of starting material can be seen in the  $^1\text{H}$  NMR.

### 3.3 Reaction Scope of Enol Ethers

With the optimal reaction conditions successfully identified the scope of the rearrangement can be investigated further. The initial rearrangement product **252a** features a  $\beta$ -methoxy group. It was hoped to establish the generality of this rearrangement, and show that a range of  $\beta$ -alkoxy and  $\beta$ -aryloxy compounds can be synthesised. Included in these will be protecting groups, which should allow easy access to  $\beta$ -hydroxy groups, a more common motif in natural products than their protected derivatives.

#### 3.3.1 Substrate Synthesis

With the chiral oxazolidine synthesis already completed, attention was focused on the enol ether portion of the substrate. For all our previous investigations (*E*)-3-methoxyprop-2-en-1-ol (or methoxy enol ether) **218a** has been used due to the commercial availability of its precursor methyl *trans*-3-methoxyacrylate. However, for substitution other than methyl it is necessary to synthesise these vinylogous esters. Work into this synthesis has already been conducted within the laboratory, where several reagents were investigated as catalysts in the 1,4-addition of oxygen nucleophiles to activated acetylenes (Table 17).<sup>179</sup>

Table 17 - 1,4-Addition optimization<sup>179</sup>

COC(=O)C#C (253)  $\xrightarrow[\text{THF, RT, Time}]{\text{tPrOH (1.1 eq), Catalyst (10 mol%)}}$  COC(=O)C=COiPr (217c)

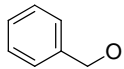
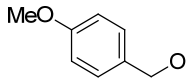

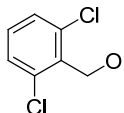

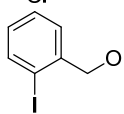

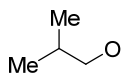
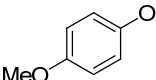

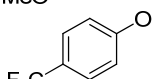

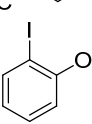
Entry	Catalyst	Time	Yield	Comments
1	NMM	4 hrs	65%	Homo coupling observed
2	P( <sup><i>n</i></sup> Bu) <sub>3</sub>	24 hrs	74%	Purification by distillation
3	DABCO	0.5 hrs	73%	Purification by chromatography

Of these previously reported methods,<sup>193-195</sup> the DABCO-mediated reaction provided the desired products in good yields, along with short reaction times, and required the simplest purification techniques. For these reasons this was the method of choice.



With a suitable route developed, several alcohols were reacted with methyl propiolate to afford a range of vinylogous esters **217b-p** (Table 18).

**Table 18 - DABCO catalysed 1,4-addition into methyl propiolate**

$  \begin{array}{ccc}  \text{MeO}_2\text{C}-\text{C}\equiv\text{C} & \xrightarrow[\text{THF, RT, 30 min}]{\text{ROH (1.1 eq), DABCO (10 mol\%)}} & \text{MeO}_2\text{C}-\text{CH}=\text{CH}-\text{OR} \\  \mathbf{253} & & \mathbf{217b-p}  \end{array}  $							
Entry	OR	Product	Yield	Entry	OR	Product	Yield
1	OEt	<b>217b</b>	88%	9		<b>217j</b>	86%
2	O <sup>i</sup> Pr	<b>217c</b>	73%	10		<b>217k</b>	93%
3		<b>217d</b>	85%	11		<b>217l</b>	62%
4		<b>217e</b>	86%	12		<b>217m</b>	91%
5		<b>217f</b>	98%	13		<b>217n</b>	86%
6		<b>217g</b>	91%	14		<b>217o</b>	36%
7		<b>217h</b>	93%	15		<b>217p</b>	81%
8		<b>217i</b>	93%				

The range of alcohols reacted with methyl propiolate **253** successfully, to afford the desired vinylogous carbonates in good to excellent yields (62-93%). The only low yielding reaction was with cyclohexanol, where 36% yield was observed. Steric effects can be reasonably discounted, since *iso*-propyl **217c** and **217p**, both synthesised from secondary alcohols, are formed in good yields.

Having already established the optimum conditions and work-up procedure for the DIBAL-H reduction of these class of vinylogous carbonates using methyl *trans*-3-methoxyacrylate (Scheme 52), all the vinylogous carbonates were subjected to these reaction conditions (Table 19).

Table 19 - DIBAL-H reduction of vinylogous carbonates

$$\text{MeO}-\text{C}(=\text{O})-\text{CH}=\text{CH}-\text{OR} \xrightarrow[\text{Tol., } -78\text{ }^\circ\text{C}]{\text{DIBAL-H (2.5 eq)}} \text{HO}-\text{CH}_2-\text{CH}=\text{CH}-\text{OR}$$

**217a-p** **218a-p**

Entry	OR	Product	Yield	Entry	OR	Product	Yield
1	OMe	<b>218a</b>	77%	9		<b>218i</b>	82%
2	OEt	<b>218b</b>	88%	10		<b>218j</b>	80%
3	O <sup>i</sup> Pr	<b>218c</b>	76%	11		<b>218k</b>	90%
4		<b>218d</b>	71%	12		<b>218l</b>	91%
5		<b>218e</b>	83%	13		<b>218m</b>	89%
6		<b>218f</b>	53%	14		<b>218n</b>	86%
7		<b>218g</b>	64%	15		<b>218o</b>	74%
8		<b>218h</b>	95%	16		<b>218p</b>	72%

Despite the sensitivity of these compounds generally good yields were seen across the board, and, providing they were stored below 0 °C and under nitrogen gas, storage was possible for several months without decomposition.

Carbodiimide promoted esterification allowed the successful synthesis of the desired allylic oxazolidine esters **251a-p** (Table 20). The same optimized conditions were used as have been seen for both the phthalimide protected substrates, and the heteroproline derivatives. In the majority of cases purification was through a short pad of either base treated silica, or basic alumina. However, three of the substrates proved to be particularly sensitive, and were not amenable to further purification. For this reason, the *ortho*-iodobenzyl-, *iso*-butyl-, and cyclohexyl- substrates (**217m**, **217n**, **217o** respectively) were taken forward into the rearrangement without any purification, and used in their crude form. A fourth, the *iso*-propyl **217c** suffered heavy decomposition on

the column, however, it was possible to isolate sufficient pure product to be used in the rearrangement.

**Table 20 - Allylic oxazolidine ester synthesis**

Entry	OR	Product	Yield
1	OMe	<b>251a</b>	91%
2	OEt	<b>251b</b>	93%
3	O <sup>i</sup> Pr	<b>251c</b>	36%
4		<b>251d</b>	75%
5		<b>251e</b>	79%
6		<b>251f</b>	83%
7		<b>251g</b>	84%
8		<b>251h</b>	95%
9		<b>251i</b>	72%
10		<b>251j</b>	74%
11		<b>251k</b>	51%
12		<b>251l</b>	60%
13		<b>251m</b>	-
14		<b>251n</b>	-
15		<b>251o</b>	-
16		<b>251p</b>	83%

### 3.3.2 Substrate Rearrangement

With a wide variety of allylic oxazolidine esters prepared, the scope of the rearrangement could be investigated, following the optimised rearrangement protocol.

**Table 21 - Rearrangement scope: alkoxy enol ether variation**

Reaction scheme: **251a-e** (oxazolidine ester with allylic OR group)  $\xrightarrow[2) \text{CH}_2\text{N}_2, \text{Et}_2\text{O}]{1) \text{TMSCl (3 eq), LHMDS (3 eq), THF, -78 }^\circ\text{C to RT}}$  **252a-e** (rearranged oxazolidine ester with OR group)

Entry	OR	Product	Yield	dr <sup>[a]</sup>
1	OMe	<b>252a</b>	78%	>99:1
2	OMe	<i>rac</i> - <b>252a</b> <sup>[b]</sup>	81%	>99:1
3	OMe	<i>ent</i> - <b>252a</b> <sup>[c]</sup>	83%	>99:1
4	OEt	<b>252b</b>	84%	>99:1
5	O <sup>i</sup> Pr	<b>252c</b>	70%	>99:1
6		<b>252d</b>	71%	>99:1
7		<b>252e</b> <sup>[d]</sup>	76%	>99:1

<sup>[a]</sup> Measured by <sup>1</sup>H NMR (500 MHz) analysis of crude reaction mixture. <sup>[b]</sup> Oxazolidine derived from DL-serine. <sup>[c]</sup> Oxazolidine derived from D-serine. <sup>[d]</sup> Isolated as TMS alkyne.

The rearrangement protocol is seen to be general, with yields between 47-84%, and excellent diastereoselectivity seen for all examples. A large variety of *O*-functionality has been examined, with simple alkyl substrates (Table 21 entries 1-4) rearranging with the highest yields. Increasing the substitution on these alkyl groups (entry 5) lowers the yield slightly, but importantly doesn't alter the diastereoselectivity. Functionalised alkyl groups are tolerated well, with the allyl ether **251d** rearranging in good yield (entry 6). Rearrangement of the propargylic substrate **251e** results in the silylation of the terminal alkyne, with the TMS alkyne isolated (entry 7). This silylation can be accounted for by the excess levels of both base, and TMSCl present in the reaction mixture.

Table 22 - Rearrangement scope: aryl enol ether variation

	<b>251f-I</b>		<b>252f-I</b>	
Entry	OR	Product	Yield	dr. <sup>[a]</sup>
1		<b>252f</b>	77%	>99:1
2		<b>252g</b>	68%	>99:1
3		<b>252h</b>	73%	>99:1
4		<b>252i</b>	58%	>99:1
5		<b>252j</b>	73%	>99:1
6		<i>rac</i> - <b>252j</b> <sup>[b]</sup>	73%	>99:1
7		<i>ent</i> - <b>252j</b> <sup>[c]</sup>	72%	>99:1
8		<b>252k</b>	75%	>99:1
9		<b>252l</b>	70%	93:7

<sup>[a]</sup> Measured by <sup>1</sup>H NMR (500 MHz) analysis of crude reaction mixture. <sup>[b]</sup> Oxazolidine derived from DL-serine. <sup>[c]</sup> Oxazolidine derived from D-serine.

The rearrangement can also be successfully applied to aryl and benzyl based enol ethers, which allows easy access to a range of β-aryloxy-α-amino acids. A wide range of hydroxyl protecting groups (Table 22 entries 2, 5-8) can be successfully incorporated into the rearrangement, hence allowing a range of deprotection options. Gratifyingly this rearrangement has also shown good tolerance to *O*-functional handles (Table 22 entry 4 & Table 23 entry 1), which shows the potential for further synthetic elaboration.

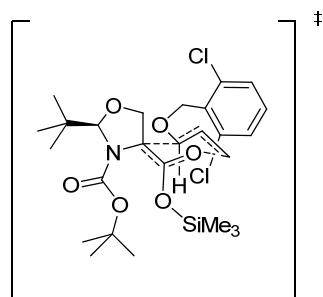
**Table 23 - Rearrangement scope: sensitive substrates – 2 step reactions**

Entry	OR	Product	Yield	dr <sup>[a]</sup>
1		<b>252m</b>	51% <sup>[b]</sup>	>99:1
2		<b>252n</b>	55% <sup>[b]</sup>	>99:1
3		<b>252o</b>	47% <sup>[b]</sup>	>99:1

<sup>[a]</sup> Measured by <sup>1</sup>H NMR (500 MHz) analysis of crude reaction mixture. <sup>[b]</sup> Yields based on **218m-o**.

In the case of the *iso*-butyl- and cyclohexyl ethers, in addition to the *ortho*-iodo benzyl ether the yields shown are over two steps; the first being the carbodiimide esterification. Taking into account the yield of ester formation these rearrangements have been shown to rearrange as efficiently as the other examples (70-80%).

The only substrate not to furnish a single diastereomer is dichlorobenzyl ether **252l** (Table 22 entry 9). Here, we see a slight drop in diastereoselectivity to 93:7. A potential explanation for this is that the di-substituted nature of the aromatic ring is starting to disfavour the chair transition state (Figure 23).

**Figure 23 - Proposed chair transition state**

The absolute and relative stereochemistry obtained in this Ireland-Claisen rearrangement has been confirmed by X-ray diffraction of the iodoaryl ether **252i** (Figure 24). The sense of stereochemistry observed is consistent with the expected transition state, where the enol ether portion approaches the silylketene acetal *anti* to the *tert*-butyl group of the oxazolidine. Furthermore, this approach is consistent with other stereochemical transformations that utilise Seebach's self-regeneration of stereocentres method.<sup>90, 196-202</sup>

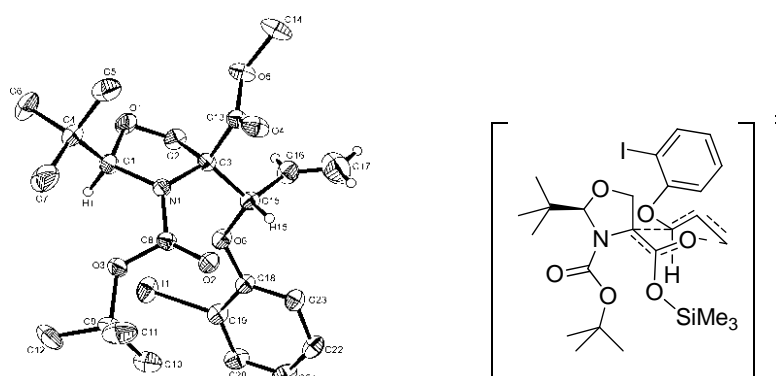
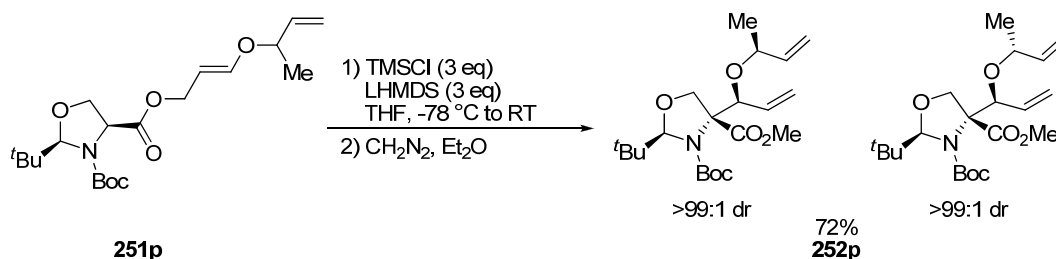


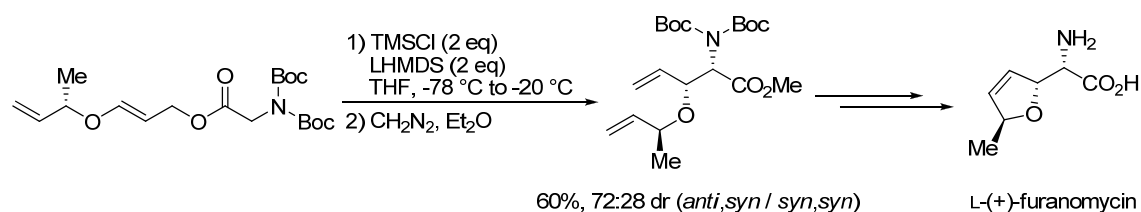
Figure 24 - ORTEP plot of XRD analysis of **252i** with proposed Ireland-Claisen rearrangement geometry

Whilst technically isolated as a 1:1 mixture of diastereomers, rearrangement of the substituted methallyl substrate **251p** proceeds as a single diastereomer with respect to the new stereocentres being formed (Scheme 74).



Scheme 74 - Rearrangement of racemic enol ether

In an analogous rearrangement, utilising an *N*-diboc glycine derived substrate, this ether substitution has been used in the formal synthesis of L-(+)-furanomycin (Scheme 75).<sup>174</sup> It follows that this would allow **252p** to present a novel analogue to this natural antibiotic.<sup>203-204</sup>



Scheme 75 - Synthesis of L-(+)-furanomycin

Diazomethane esterification has been an integral part of the rearrangement protocol, allowing for ease of isolation and characterisation as the methyl ester. However, whilst it is quick, efficient, and easy to incorporate into the experimental procedure there are times when alternative ester groups could be required. A benzyl ester would offer the potential for rapid removal under hydrogenation conditions, and, in conjunction with the benzyl ether **252j** allows for global deprotection. As an alternative to diazomethane, benzyl bromide can be used to synthesise this desired ester (Table 24).

Table 24 - Rearrangement scope: benzyl ester synthesis

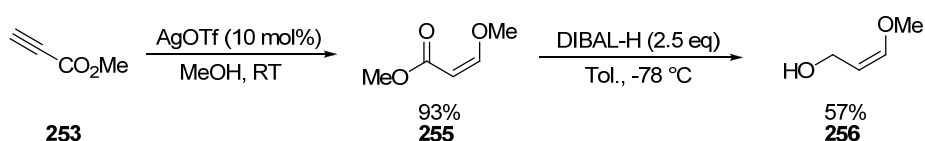
Entry	OR	Product	Yield	dr. <sup>[a]</sup>
1		<b>254j</b>	72%	>99:1
2		<i>ent</i> - <b>254j</b> <sup>[b]</sup>	60%	>99:1
3		<b>254k</b>	58%	>99:1
4		<i>ent</i> - <b>254k</b> <sup>[b]</sup>	60%	>99:1

<sup>[a]</sup> Measured by <sup>1</sup>H NMR (500 MHz) analysis of crude reaction mixture. <sup>[b]</sup> Oxazolidine derived from D-serine.

In general, there is a small decrease in yield in forming the benzyl ester when compared to the methyl ester. This suggests that the esterification is not as efficient when using benzyl bromide instead of diazomethane.

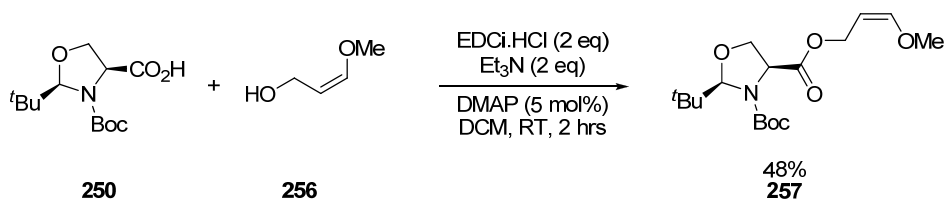


With a range of enol ethers demonstrating the reliability of this rearrangement, we wanted to test the limits. All previous examples use *E*-enol ethers. If the transition state geometry holds, use of a *Z*-enol ether should give rise to the alternate diastereomer. Whilst the route to the required *Z*-substrate is broadly similar as seen for the *trans* olefins, the addition to methyl propiolate is now conducted using a catalytic amount of silver(I) trifluoromethanesulfonate (Scheme 76).<sup>205</sup> Reduction with DIBAL-H in toluene follows the same procedure used with the *E*-enol ethers.



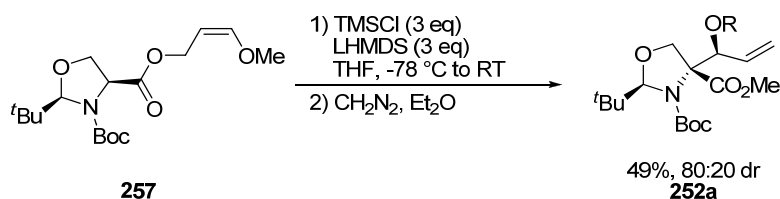
Scheme 76 - Synthesis of (*Z*)-3-methoxyprop-2-en-1-ol

Subsequent carbodiimide esterification with the oxazolidine acid **250** proceeded in moderate yield (Scheme 77). Substrate **257** proved to be more sensitive than the *trans* derivative, and this can account for the lost mass during purification.



Scheme 77 - Carbodiimide promoted synthesis of *Z*-methoxyallyl oxazolidine ester **257**

The substrate was subjected to the rearrangement conditions, with the expectation that formation of the opposite diastereomer would be seen. However, this was not fully the case. Instead, a mixture of diastereomers were seen, with the major diastereomer the same as observed in the rearrangement of the *trans*-substrate, in an 80:20 diastereomeric ratio (Scheme 78).



Scheme 78 - Rearrangement of *Z*-enol ether

We can hypothesise that the *Z*-enol ether is now sitting in an axial position in the chair transition state (Figure 25), increasing 1,3-allylic strain, and consequently reducing the rate of the reaction. Due to the high electron density around the enol ether, it is possible that a significant quantity of substrate is undergoing isomerisation to the *E*-enol ether, which, when formed, reacts faster than its *Z*-isomer to produce the diastereoselectivity seen.

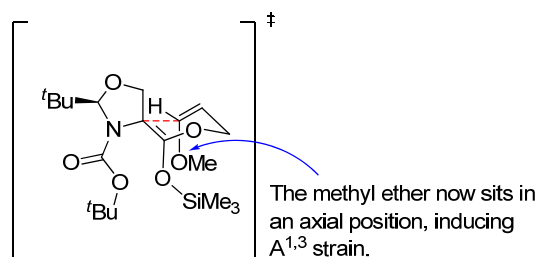
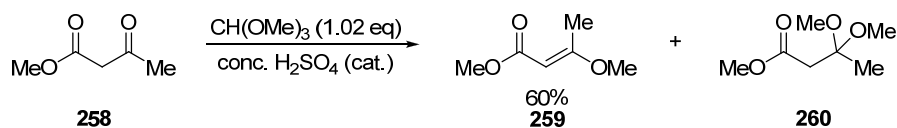


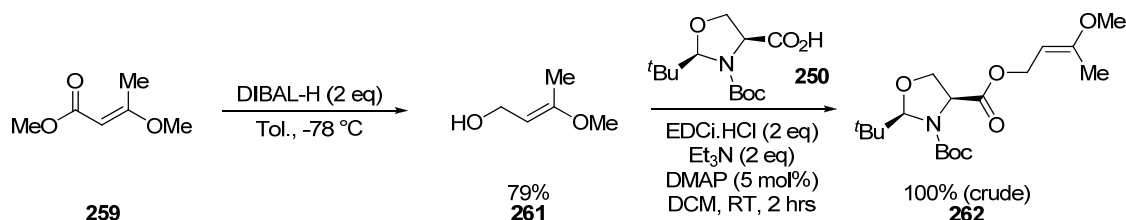
Figure 25 - Postulated transition state for the *Z*-enol ether

To probe how this 1,3-allylic strain effects the rearrangement 1,2,2'-trisubstituted enol ether **261** was synthesised and coupled to the oxazolidine acid **250**.



Scheme 79 - Synthesis of (*E*)-methyl 3-methoxybut-2-enoate

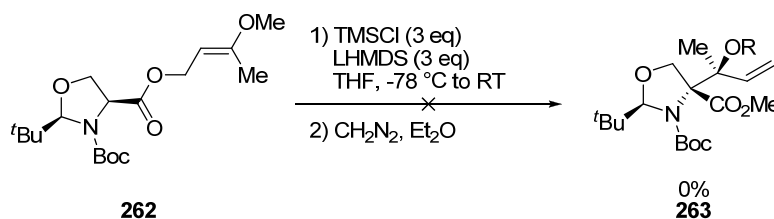
The trisubstituted vinylogous carbonate **259** was obtained in a 60% yield, along with a small quantity of side product **260** (Scheme 79).<sup>206</sup>



Scheme 80 - Synthesis of trisubstituted oxazolidine allyl ester

This was then reduced using DIBAL-H to afford the enol ether **261** in excellent yield (Scheme 80). The final step in the substrate synthesis was carbodiimide coupling to afford **262** in a quantitative yield. Due to the stability of the substrate, attempts at

purification were abandoned, and the substrate was taken forward to the rearrangement in a crude form.



**Scheme 81 - Unsuccessful rearrangement of (2*R*,4*S*)-3-*tert*-butyl 4-((*E*)-3-methoxybut-2-enyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate**

Attempts at rearranging this trisubstituted substrate proved ineffective. The standard conditions failed to show any sign of product, with just starting material seen by TLC. Extended reaction times, and increasing the final reaction temperature to 40 °C failed to produce any conversion.

Whilst the rearrangement itself was ultimately unsuccessful, it does allow further insight into the course of the reaction, and help to demonstrate the effect that a *Z*-substituted olefin has on the reaction; that the 1,3-allylic strain is such that the rearrangement is not favourable. In the case of the *Z*-enol ether rearrangement (Scheme 78), this helps to corroborate the hypothesis that isomerisation to the *E*-enol ether after slow rearrangement of the *Z*-enol ether is the cause of the low level of diastereoselectivity seen.

### 3.4 Reaction Scope of Crotyl Esters<sup>207</sup>

With a range of enol ether derived substrates (**251a-p**) successfully rearranged, highlighting the synthetic applicability of this rearrangement protocol, efforts turned to developing this reaction further. It is known that the increased electron density provided by the oxygen in the enol ether helps to promote rearrangement, and increase the rate of rearrangement.<sup>153, 208-209</sup> Despite this, it was hoped that the rearrangement procedure was robust enough to be applicable to carbon substituted allyl groups. This would present an enantiomeric approach to  $\beta$ -hydroxy- $\alpha$ -amino acid derivatives of proteinogenic amino acids leucine and isoleucine – alongside more unnatural amino acids – from the abundant amino acid serine.

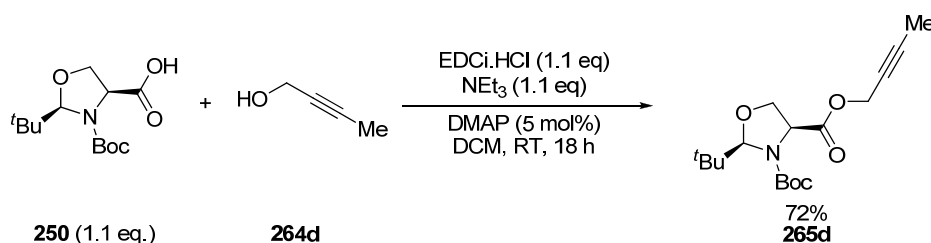
### 3.4.1 Substrate Synthesis

Featuring the same chiral oxazolidine core, a range of commercially available alcohols were used to synthesise the required allyl esters for the Ireland-Claisen rearrangement. In all previous carbodiimide promoted esterification reactions, two equivalents of the oxazolidine carboxylic acid were used to one equivalent of the enol ether. However, since commercial alcohols are now being used, it was desirable to conserve as much of the synthetically produced acid as possible. For this reason, the equivalents were dropped from 2 to just 1.1 in all cases.<sup>210</sup>

**Table 25 - Synthesis of oxazolidine allylic ester rearrangement substrates**

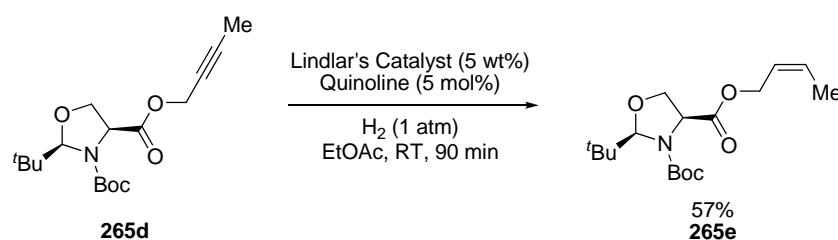
Entry	R <sup>1</sup>	R <sup>2</sup>	Product	Yield
1	H	H	<b>265a</b>	84%
2	H	Me	<b>265b</b>	84%
3	Me	H	<b>265c</b>	97%

All three substrates were successfully synthesised, without the need for further purification, and in excellent yields. Whilst the *E*-crotyl alcohol **264b** is readily available, the same cannot be said for its isomer *Z*-crotyl alcohol. In order to synthesise the *Z*-crotyl substrate, a new approach was necessary.



**Scheme 82 – Carbodiimide coupling of oxazolidine and 2-butyne-1-ol**

Carbodiimide coupling of 2-butyn-1-ol with the oxazolidine **250** furnished alkyne substrate **265d** in good yield (Scheme 82). Whilst this allows entry into the *Z*-crotyl substrate through hydrogenation using Lindlar's catalyst (Scheme 83), it also presents an opportunity to test the rearrangement protocol on an alkyne rather than the typical allyl esters seen in Ireland-Claisen rearrangements.



Scheme 83 - Lindlar hydrogenation of 2-butyne oxazolidine ester

### 3.4.2 Substrate Rearrangement

With the Ireland-Claisen rearrangement substrates prepared they were subjected to the conditions previously optimised for the enol ether based substrates.

Table 26 - Rearrangement scope: carbon substitution

Entry	OR <sup>1</sup>	R <sup>2</sup>	Product	Yield	dr <sup>[a]</sup>
1			<b>266a</b>	57%	>99:1
2			<b>266b</b>	44%	>99:1
3			<b>266c</b>	26% <sup>[b]</sup>	>99:1
4			<b>266d</b>	56%	>99:1
5			<b>266e</b>	0% <sup>[b]</sup>	-

<sup>[a]</sup> Measured by <sup>1</sup>H NMR (500 MHz) analysis of crude reaction mixture. <sup>[b]</sup> Reactions stirred for an additional 72 hours at 65 °C.

It can immediately be seen that the yields are much lower, and reaction times longer, than those for the enol ether rearrangements, which is consistent with the electronic effects predicted. Nonetheless, the rearrangement does work, and single diastereomers are produced in each instance. That is, the reaction is consistent with the approach of the silylketene acetal *anti* to the oxazolidine *tert*-butyl group. The additional stereocentre created in the case of the *E*-crotyl rearrangement is also formed stereoselectively. This indicates that silylketene acetal formation occurs stereoselectively. To achieve any conversion for the 2-methyl propen-ester **266c** it was necessary to extend the reaction time by 72 hours in conjunction with heating to 65 °C. The only substrate which does not undergo rearrangement (even after heating) is the *Z*-crotyl ester. This mirrors the results seen in the rearrangements of the *E*- and *Z*-methoxy enol ether substrates (**252a** and **257**), whereby the 1,3-allylic strain appears to significantly retard the rate of reaction. In this case it completely stops any reaction from taking place.

Rearrangement of the alkyne ester presents an intriguing product. Allene **266d** formed large translucent crystals which enabled a crystal structure to be obtained allowing confirmation of the stereochemical outcome of the rearrangement (Figure 26). Allenes are a very versatile functional group, and are found in many natural products.<sup>211-212</sup> Not only can they act as either an electrophile<sup>213</sup>, or a nucleophile<sup>214</sup>, but are also commonly used in cycloaddition reactions.<sup>215-216</sup>

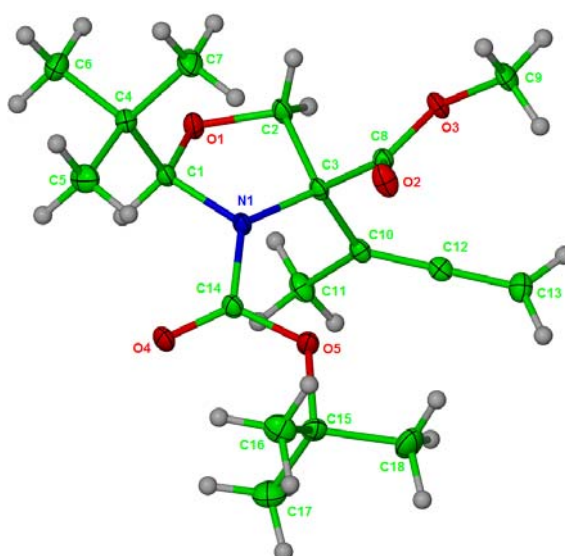


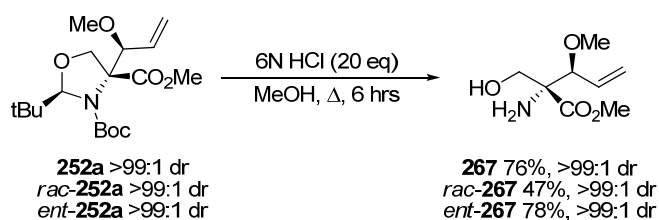
Figure 26 - XRD analysis of allene **266d**

### 3.5 Rearrangement Product Derivatisation

The products obtained through this rearrangement protocol allow plenty of scope for further synthetic elaboration. Whilst the products obtained from the enol ether containing substrates allow deprotection, in addition to elaboration of the ether functionality, the products obtained from the rearrangement of the carbon substituted allyl esters allow for the synthesis of  $\beta$ -hydroxy- $\alpha$ -amino acid derivatives of some natural proteinogenic amino acids.

#### 3.5.1 Derivatisation of Enol Ether Rearrangement Products

Whilst the potential for synthetic elaboration on the range of compounds **252a-p** is quite vast, the initial principle which forms the basis of the self-regeneration of stereocentres methodology is the ability to remove the temporary stereocentre that provided the control of chirality. In this case, this means acid hydrolysis of the oxazolidine with concomitant deprotection of the Boc group (Scheme 84).<sup>217</sup> Gratifyingly, there is no loss of diastereoselectivity under the reaction conditions.

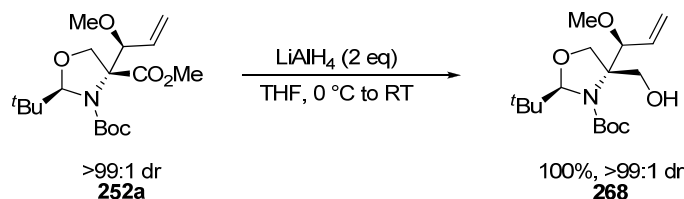


**Scheme 84 - Acid hydrolysis of *N*-Boc oxazolidine rearrangement product**

With successful hydrolysis of the oxazolidine, the principle of SRS has been upheld. That is, a temporary stereocentre has been installed, creation of an achiral  $sp^2$  reactive site has resulted in a diastereoselective reaction, and removal of the temporary stereocentre has been completed. Knowing that the process has gone full circle a range of synthetic manipulations can be conducted to highlight the potential that these substrates hold.

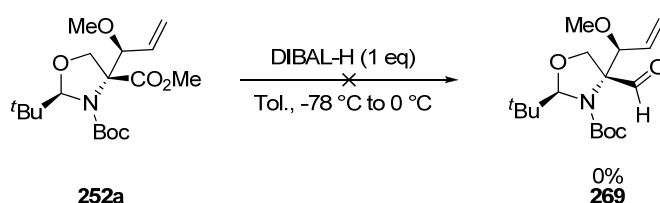
### Reduction of Ester Functionality

The methyl ester that results after diazomethane esterification is amenable to reduction through the use of lithium aluminium hydride to afford the primary alcohol in a quantitative yield. As was observed in the hydrolysis of **252a**, there was no loss of diastereoselectivity in the reaction with a single diastereomer seen for the primary alcohol **268**.



Scheme 85 - Lithium aluminium hydride reduction of oxazolidine methyl ester

An attempt was made at the selective DIBAL-H reduction of the oxazolidine methyl ester **252a** to the methyl ketone, however after 4 hours at -78 °C there was no indication by TLC analysis of any reduction products. The reaction was allowed to warm to 0 °C where it was stirred for a further 3 hours. There being no sign of any product formation, the reaction mixture was quenched with an ethyl acetate/Rochelle Salt solution and starting material **252a** was recovered.



Scheme 86 - Attempted DIBAL-H reduction to oxazolidine methyl ketone

### Ring Closing Metathesis

Ring closing metathesis is a key C-C bond forming reaction, which has become an essential tool in the synthesis of natural products over the last quarter of a century.<sup>218</sup> Robert Grubbs has been instrumental in the development of this field, and it was his group which developed a series of air-stable ruthenium-based carbene catalysts that, whilst less active than other systems, exhibit far greater functional group tolerance, allowing for new synthetic applications.<sup>219-220</sup>



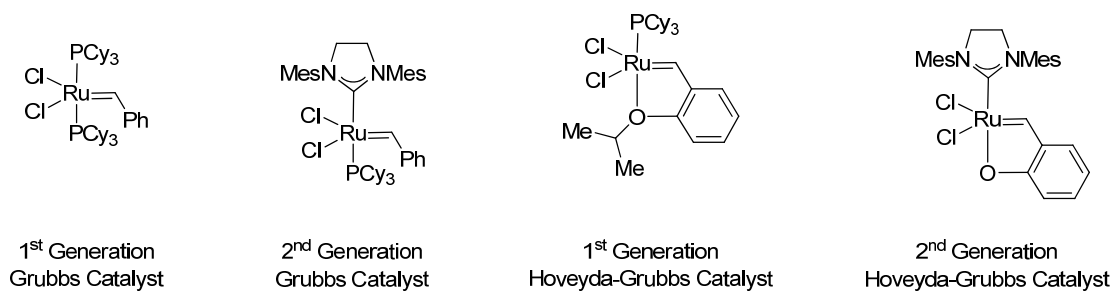
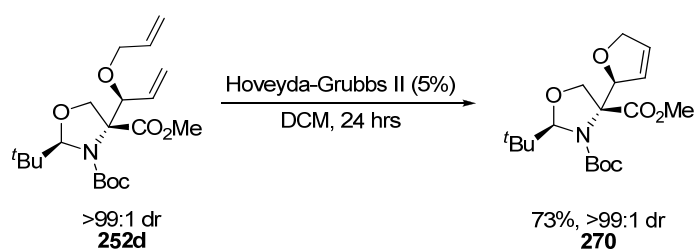


Figure 27 - Structures of ruthenium-based metathesis catalysts

On subjecting the allyl ether **252d** to the second generation Hoveyda-Grubbs catalyst in dichloromethane for 24 hours, 2,5-dihydrofuran **270** was obtained in good yield.

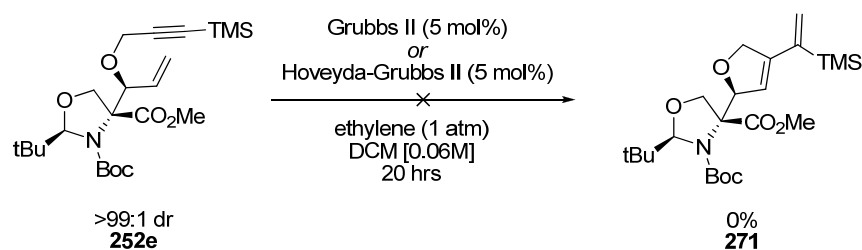


Scheme 87 - 2,5-Dihydrofuran synthesis *via* ring closing metathesis

Such dihydrofurans and their derivatives can be found in polyether antibiotics and mycotoxins and can therefore be seen to be an important class of compounds.<sup>221-225</sup>

### Enyne Metathesis

Enyne metathesis bears the same mechanistic rationale as alkene metathesis, and can be considered to be a bond reorganisation of an alkene and an alkyne to produce 1,3-dienes.<sup>226</sup>

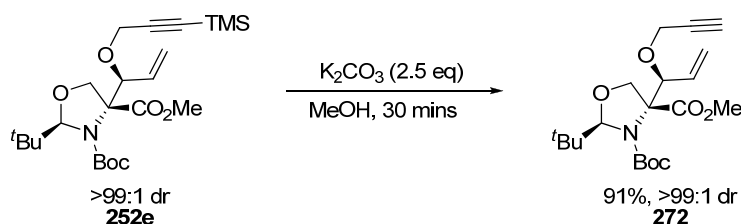


Scheme 88 - Attempted enyne metathesis on trimethylsilyl alkyne **252e**

Alkyne **252e** is the perfect substrate on which to attempt an enyne metathesis. The metathesis was attempted with both Grubbs II and Hoveyda-Grubbs II catalysts,

however unfortunately with the trimethylsilane group present there is no reaction, and the starting alkyne is the sole compound isolated from the reaction mixture.

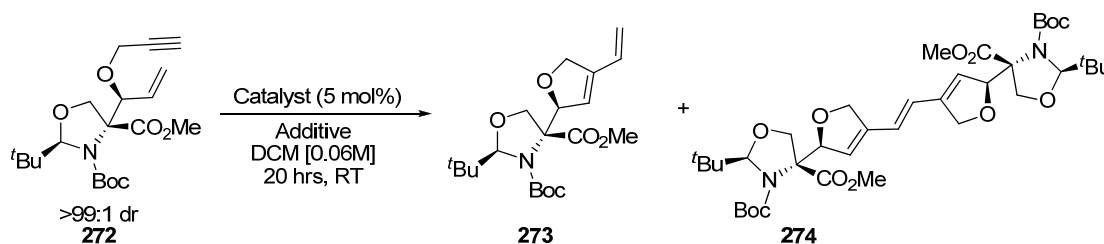
It is possible that the presence of the silyl group on the alkyne is preventing the metathesis from taking place. Removal of the silyl group through the use of potassium carbonate in methanol afforded the desired terminal alkyne **272** in excellent yield.



**Scheme 89 - Deprotection of TMS alkyne**

In 1998 Mori reported the dramatic effect ethylene can have on the yield of ruthenium catalysed enyne RCM reactions.<sup>227</sup> Furthermore, Smulik and Diver have previously shown that alkynes that undergo poor enyne metathesis perform better when the second generation of Grubbs' ruthenium catalyst is used.<sup>228</sup>

**Table 27 - Initial optimisation screen for enyne metathesis catalysts**



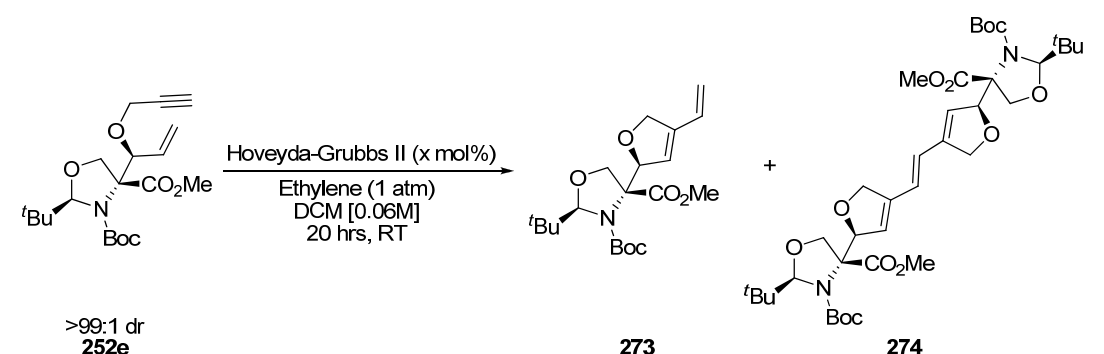
Entry	Catalyst	Additive	Yield 273 (%)	Yield 274 (%)
1	Grubbs I	-	0	0
2	Grubbs I	allyl alcohol (5 mol%)	0	0
3	Grubbs I	ethylene (1 atm)	trace	trace
4	Grubbs II	ethylene (1 atm)	50	50
5	Hoveyda-Grubbs II	ethylene (1 atm)	50	50
6 <sup>[a]</sup>	Hoveyda-Grubbs II	ethylene (1 atm)	50	50

<sup>[a]</sup> Reaction complete after 10 hours.

An initial screen of ruthenium catalysts, along with a selection of additives (Table 27) mirrored that seen by Smulik and Diver; that the first generation catalyst showed only a trace amount of conversion, and only when in the presence of ethylene. When the carbene based 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene-substituted ruthenium complex (Grubbs II) was used complete consumption of starting material was seen after 20 hours. However, in addition to seeing the desired 1,3-diene **273**, the dimer **274** was also isolated, in a 1:1 mass ratio. The Hoveyda-Grubbs II catalyst showed the ratio and yields between the monomer and dimer as seen with the Grubbs II catalyst, however the rate of the reaction was quicker.

Attempts were made to limit the amount of dimer being produced from the cross-metathesis of the initially formed monomer. Unfortunately, whilst lowering the catalyst loading increased the ratio slightly in favour of the monomer, it left a considerable quantity of starting material present.

**Table 28 - Effect of catalyst loading on monomer:dimer ratio**

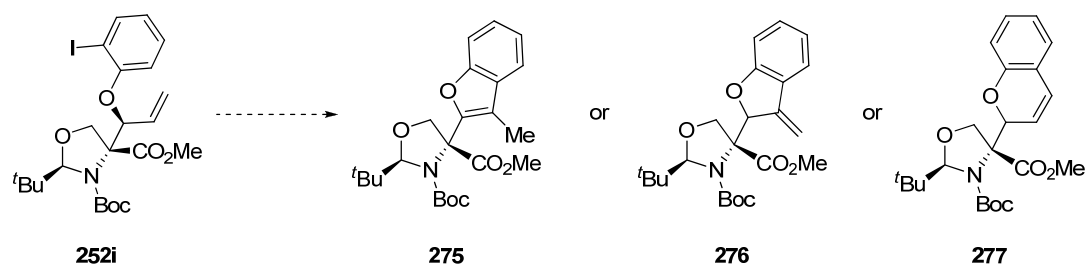


Entry	Catalyst	Loading (x mol%)	Yield 273 (%)	Yield 274 (%)
1	Hoveyda-Grubbs II	5	50	50
2	Hoveyda-Grubbs II	2.5	31	25
3	Hoveyda-Grubbs II	1.25	10	6

### Heck Reaction

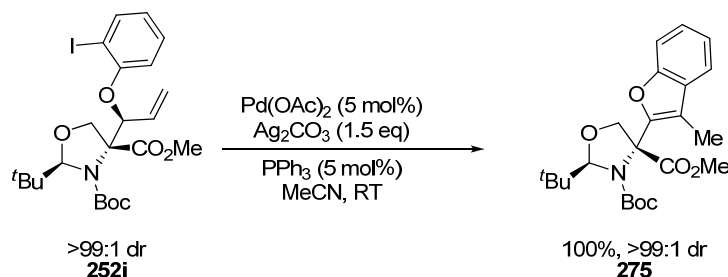
The intramolecular Heck reaction of the *ortho*-iodophenoxy rearrangement product **252i** has the potential for three products to be formed; that is for either a 5-*endo*, 5-*exo*,

or 6-*endo* reaction to take place to afford the benzofuran **275**, dihydrobenzofuran **276**, or the benzopyran **277** structures respectively (Scheme 90).



**Scheme 90 - Three possible outcomes from the intramolecular Heck reaction of 252i**

The initial attempt at the Heck reaction, conducted at reflux in acetonitrile resulted in several close running spots by TLC. However, by repeating at room temperature a more controlled reaction took place. Whilst a single spot was observed by TLC, the initial  $^1\text{H}$  NMR showed there to be a mixture of two products (**275** and **276**). Fortunately, upon standing in deuterated chloroform for 2 hours, prior to a  $^{13}\text{C}$  NMR being run, isomerisation had occurred to leave the 5-*endo* product **275** as the sole product from the reaction, in a quantitative yield (Scheme 91).

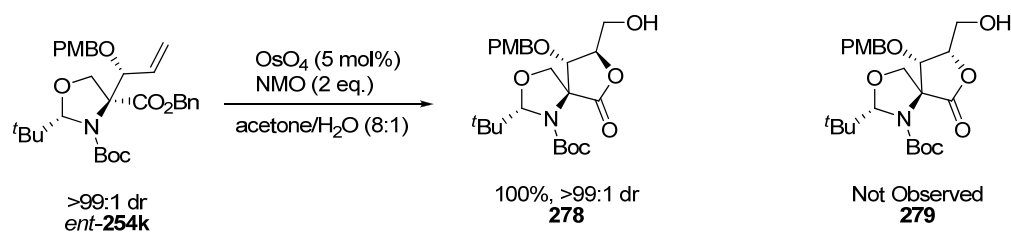


**Scheme 91 - Synthesis of a benzofuran moiety by a 5-*endo* Heck reaction**

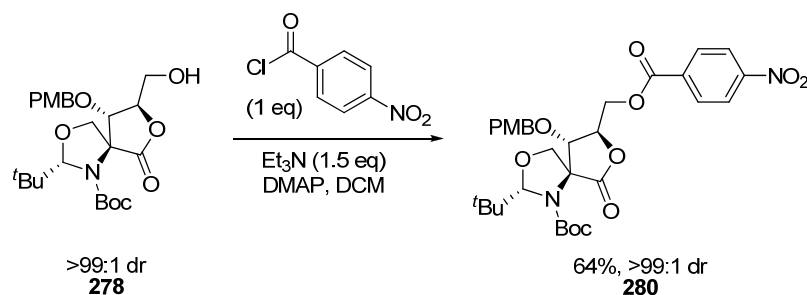
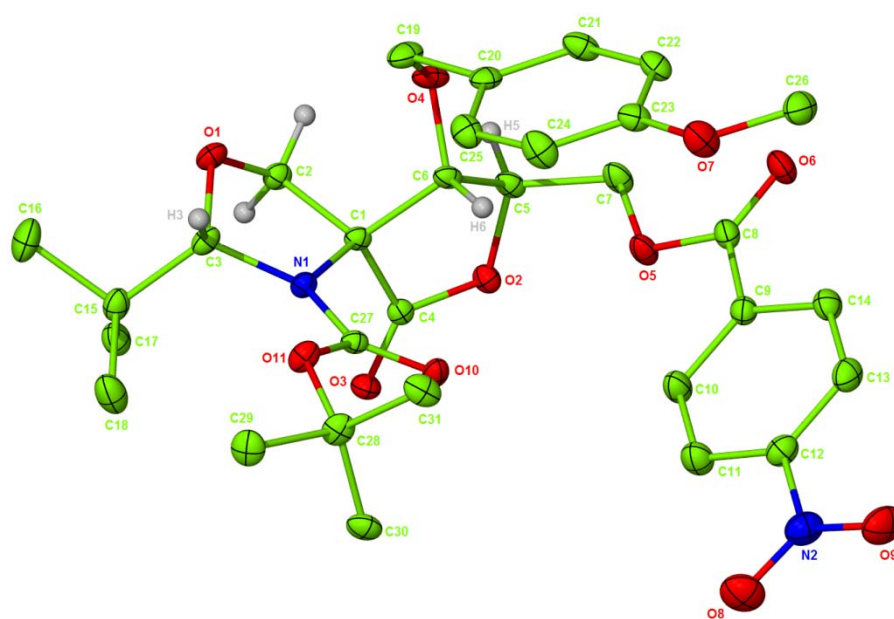
Benzofuran moieties are often found in natural products and can exhibit biological activity of interest to pharmaceutical application.<sup>229-230</sup> As such, new routes to these, and other heterocyclic compounds provide a constant challenge to the organic chemist.<sup>231</sup>

### ***Dihydroxylation***

Dihydroxylation of *para*-methoxybenzyl ether ent-**254k**, using literature conditions<sup>232</sup>, occurs with subsequent lactonisation forming either *spiro*-lactone **278** or **279** in quantitative yield, and as a single diastereomer.

Scheme 92 - Dihydroxylation to afford the  $\gamma$ -lactone

To assess the precise stereochemistry of the dihydroxylation the *para*-nitrobenzoate ester **280** was synthesised and subjected to single-crystal crystallography to obtain a definitive structure (Figure 28). From this the observed *anti* configuration of the alkene osmylation relative to the PMB ether could be assigned, and shows that *spiro*-lactone **278** was the sole product from the dihydroxylation.

Scheme 93 - Synthesis of *para*-nitrobenzoate derivative for XRD analysisFigure 28 - XRD analysis of *para*-nitrobenzoate **280**

### 3.5.2 Derivatisation of Crotyl Rearrangement Products

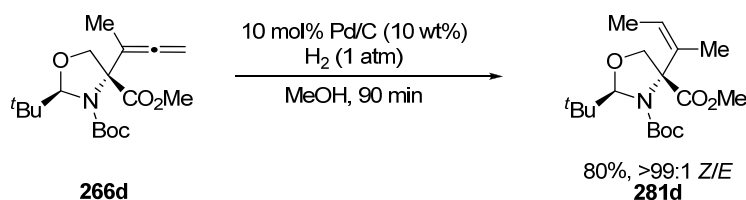
Hydrogenation of the rearrangement products enables access to the amino acid side chains that feature on some proteinogenic amino acids.

**Table 29 – Hydrogenation of crotyl rearrangement products**

$\text{266a-c} \xrightarrow[\text{MeOH, 90 min}]{10 \text{ mol\% Pd/C (5 wt\%)}, \text{H}_2 (1 \text{ atm})} \text{281a-c}$

Entry	R <sup>1</sup>	R <sup>2</sup>	Product	Yield
1	H	H	<b>281a</b>	87%
2	Me	H	<b>281b</b>	78%
3	H	Me	<b>281c</b>	66%

All reactions went to completion in under 90 minutes with catalytic palladium on carbon under 1 atmosphere of hydrogen. Hydrogenation of the allene proceeded in just 20 minutes, to selectively afford the *Z*-alkene **281d** in an 80% yield (Scheme 94). Use of a 2D NOESY experiment allowed assignment as the *Z*- geometry (See 8.2.1 2D-NOE Spectra for 281d). Considerable interest has been shown towards vinyl glycines, due to their use as antibiotics<sup>233-234</sup>, enzyme inhibitors<sup>235</sup>, as well as synthetic intermediates<sup>236</sup>. Whilst there are many outstanding methods for the synthesis of non-proteinogenic amino acids, vinyl glycines are one highly important class for which many of these techniques cannot generally be applied.<sup>237</sup> Hence the ability to afford the asymmetric synthesis of analogues of this class of compounds is an important development.



**Scheme 94 - *Z*- Selective allene hydrogenation**

With a selection of both saturated and unsaturated protected  $\beta$ -hydroxy- $\alpha$ -amino esters synthesised, acid hydrolysis is necessary to remove the *N,O*-acetal and the Boc protecting group. The same conditions that were seen previously were also applicable to this class of compounds.

**Table 30 – Concomitant deprotection of *N,O*-acetal and Boc protecting groups**

**282a-f**

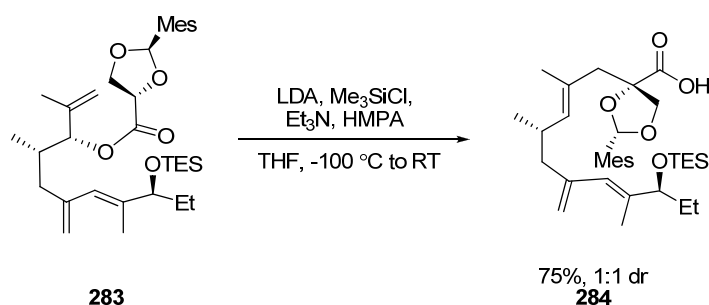
Entry	Substrate	R <sup>1</sup>	Product	Yield
1	<b>266a</b>		<b>282a</b>	80%
2	<b>266b</b>		<b>282b</b>	45%
3	<b>266d</b>		<b>282c</b>	44%
4	<b>281a</b>		<b>282d</b>	73%
5	<b>281b</b>		<b>282e</b>	59%
6	<b>281c</b>		<b>282f</b>	71%

Acid hydrolysis shows moderate to good yields across the range of substrates. Whilst the methyl ester aids isolation of these compounds, they exhibit partial solubility in aqueous solution, and this presents an area where mass could be lost in the work-up procedure.

### 3.6 Conclusions

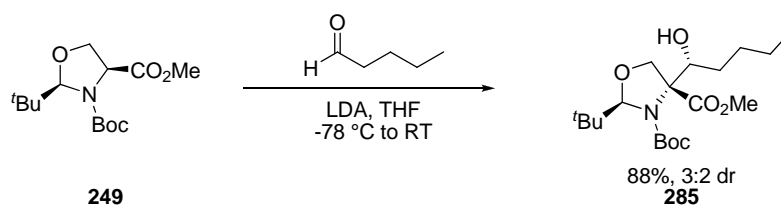
The principle of self-regeneration of stereocentres has been shown to be successfully employed in an Ireland-Claisen rearrangement to allow a highly stereospecific reaction. Not only can this novel protocol be applied to a variety of enol ether based substrates, but also those bearing carbon substitution on the allyl ester. This allows the synthesis of both  $\beta$ -hydroxy- $\alpha$ -amino acid substituted proteinogenic amino acid derivatives as well as  $\beta,\beta'$ -dihydroxy- $\alpha$ -amino acid structures that feature in a number of biologically active natural products.

There are a very limited number of Ireland-Claisen rearrangements that feature such remote transfer of chirality.<sup>116</sup> A chiral glycinate rearrangement mentioned earlier (Scheme 48) showed good levels of diastereoselectivity, whilst rearrangement of a chiral 2-mesityl-1,3-dioxolane substrate by Parsons *et al.* showed no selectivity (Scheme 95).<sup>238</sup> It can be speculated that this lack of selectivity may be due to poor *E/Z* control during silylketene acetal formation, or the lack of a ‘relay’ strategy between the two *tert*-butyl groups present in the oxazolidines featured here.



**Scheme 95 - Parsons' Ireland-Claisen rearrangement of 283**

Importantly, aldol reactions performed on an oxazolidine framework similar to that shown in this work, with simple achiral aldehydes, exhibit very low levels of diastereoselectivity (Scheme 96).<sup>192</sup> Furthermore, the ability to further functionalise such aldol products is expected to be limited due to the potential for base mediated *retro*-aldol reaction, in addition to limited nucleophilicity of the alcohol due to the proximity of sterically imposing oxazolidine moiety.



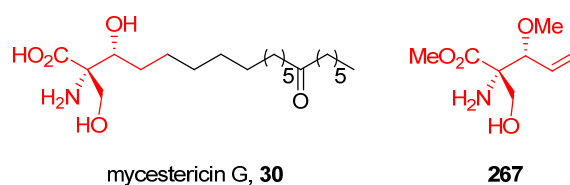
**Scheme 96 - Aldol reaction of simple achiral aldehydes with oxazolidine esters**

Shown in this context the power of this rearrangement stands out, offering exceptional stereocontrol through a self-regeneration of stereocentres strategy allowing integration of functional handles with the potential for subsequent stereoselective synthetic elaboration. As such, a range of biologically relevant natural products can now be synthesised through use of this rearrangement protocol.



## 4.1 Background

Rearrangement products **252a-p** feature a polar  $\beta,\beta'$ -dihydroxy- $\alpha$ -amino acid head group (**267**) of the kind that have been implicated by structure activity relationships as the crucial structural feature in myriocin **23**, mycestericin G **30** and other related natural products.



**Figure 29 – Mycestericin G and  $\beta,\beta'$ -dihydroxy- $\alpha$ -amino acid derived from the Ireland-Claisen rearrangement**

The *syn* stereochemistry obtained in our rearrangement (as confirmed by XRD analysis of **252i**) matches that seen in mycestericin G. The challenge posed by the compact stereochemistry and juxtaposition of the polar head and lipophilic tail make this the perfect target to apply the Ireland-Claisen methodology seen in Chapter 3.

## 4.2 Total Synthesis of Mycestericin G

### 4.2.1 Retrosynthetic Analysis

Initial examination of mycestericin G shows the potential union of the lipophilic tail, and the chiral head unit *via* cross-metathesis. The  $\beta,\beta'$ -dihydroxy- $\alpha$ -amino acid head unit will need to be synthesised from D-serine, to afford the correct enantiomer.

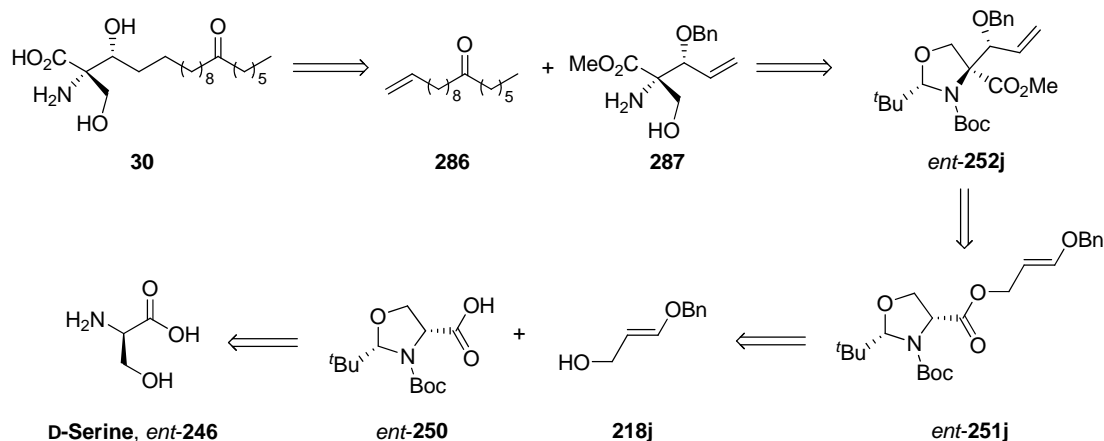


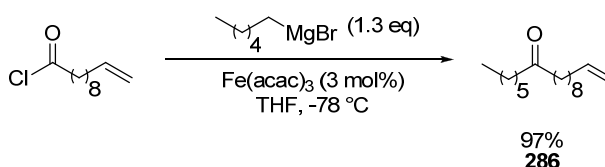
Figure 30 - Retrosynthetic analysis of mycestericin G

By utilising the benzyl ether, hydrogenation of the olefin to afford the saturated chain seen in mycestericin G should also serve to remove the benzyl protecting group. The key stereochemistry required is introduced in the rearrangement of *ent*-251j to *ent*-252j.

#### 4.2.2 Initial Investigation

Whilst the enantiomer required to complete the synthesis of (–)-mycestericin G is derived from D-serine, initial investigations were conducted using the cheaper, more readily available natural L-serine.

With a key step in the total synthesis the cross-metathesis, the lipophilic tail needs to be synthesised. Fürstner *et al.* have reported a selective iron-catalysed cross-coupling reaction of Grignard reagents with, amongst others, acid chlorides.<sup>239</sup> This provided a one step entry into a suitable cross-metathesis partner **286**.



Scheme 97 - Iron catalysed cross-coupling in the synthesis of ketone **286**

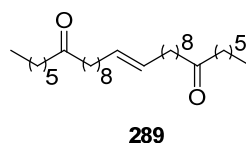
With the lipophilic coupling partner in hand, the methyl ether rearrangement product **252a** was chosen as a test substrate for the initial explorations of the cross-metathesis.

**Table 31 - Initial cross-metathesis exploration**

<b>252a</b>	<b>286</b>			<b>288a</b>
Entry	Catalyst	Temp (°C)	Time (hrs)	Conversion (%) <sup>[a]</sup>
1	Grubbs I	20	24	0
2	Grubbs II	20 to 40	24 + 24	0
3	Hoveyda-Grubbs II	40	24	50 (0)

<sup>[a]</sup> Conversion stated as product against starting material. Isolated yields shown in parenthesis

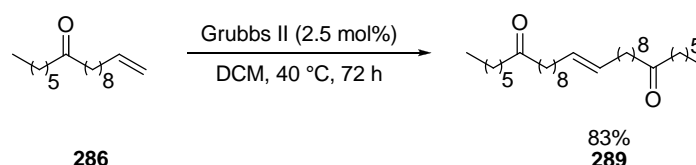
Early efforts proved unsuccessful, with neither Grubbs I nor Grubbs II catalysts showing any signs of product. It was noticed however, that a significant quantity of olefin was undergoing dimerisation, to form the homodimer **289**.

**Figure 31 - Homodimer 289**

Whilst there was an improvement on utilising the Hoveyda-Grubbs II catalyst, with a conversion of 50% seen, this was unable to be isolated due to co-elution of **252a** due to a highly similar  $R_f$ , in addition to homodimer **289** contaminating most fractions due to partial solubility in the eluent causing a slow release during chromatography.

The tolerance of cross-metathesis reactions on sterically congested olefin moieties has previously been described.<sup>240-241</sup> These reports correlate our observation that the higher activity seen in second generation [Ru]-carbenes often aids the progress of cross-metathesis reactions. However, even the use of the Hoveyda-Grubbs II catalyst proved unable to produce a clean reaction pathway. Grubbs has also demonstrated improved cross-metathesis reactions when using symmetric internal olefins.<sup>242</sup> Many cases were reported where a two-step cross-metathesis procedure whereby a terminal olefin was dimerised prior to undergoing the desired cross-metathesis reaction.

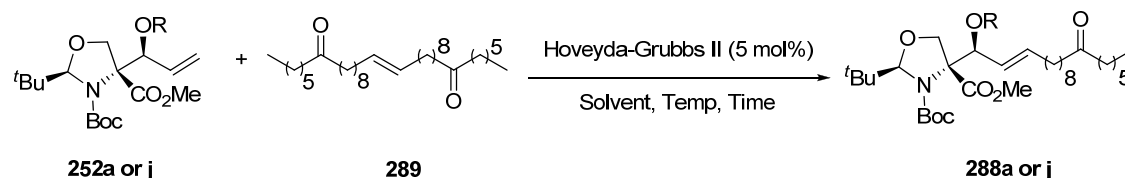
With the observation that homodimer **289** formation was facile it was decided to isolate it prior to re-attempting the desired cross-metathesis reaction (Scheme 98).



**Scheme 98 - Synthesis of homodimer 289**

The initial attempt utilising the homodimer proved successful, with 48% isolated after 72 hours (Table 32 entry 1). With a set of conditions in hand, an attempt at the cross-metathesis was made using the substrate identified in the retrosynthetic analysis, namely the benzyl ether **252j**. Disappointingly, the yield is drastically reduced, and the product is unable to be cleanly isolated. Attempts were made to optimise the cross-metathesis of the benzyl ether, however, on increasing the temperature either in toluene, or, to a lesser extent in dichloroethane, isomerisation of the homodimer is seen, and a multitude of products are seen with varying lengths of carbon in the lipophilic tail.

**Table 32 - Cross-metathesis development**

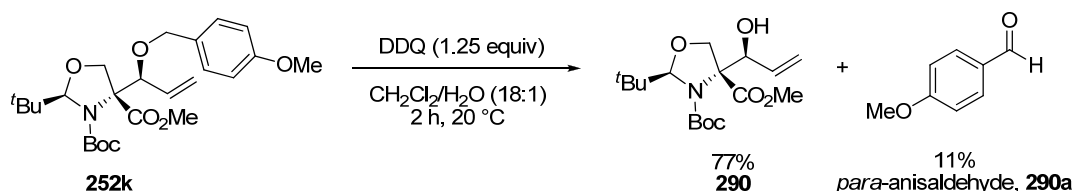


Entry	Substrate	R	Solvent	Temp (°C)	Time (hrs)	Yield (%)
1	<b>252a</b>	Me	DCM	40	72	48
2	<b>252j</b>	Bn	DCM	40	96	22 <sup>[a]</sup>
3	<b>252j</b>	Bn	Toluene	110	72	0 <sup>[b]</sup>
4	<i>ent</i> - <b>252j</b>	Bn	DCE	60	72	0 <sup>[b]</sup>

<sup>[a]</sup> Product unable to be isolated cleanly. <sup>[b]</sup> Isomerisation of **289** observed.

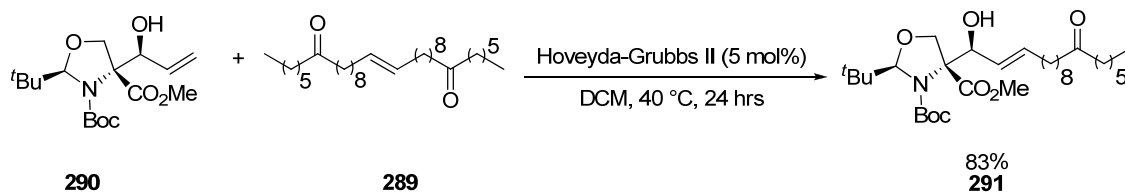
From this set of results it can be proposed that the steric bulk of the ether moiety is having a substantial effect on the outcome of the cross-metathesis. If this presumption were to hold true, then a new approach using the free hydroxyl would be expected to undergo metathesis more readily.

To this end, *para*-methoxybenzyl ether **252k** can be deprotected *via* DDQ-mediated oxidation in excellent yield. Whilst *para*-anisaldehyde **290a**, produced as a side product, proved challenging to remove by conventional methods, use as the crude reaction mixture led to no reduction in yields in subsequent synthetic steps.



Scheme 99 - DDQ deprotection of PMB ether **252k**

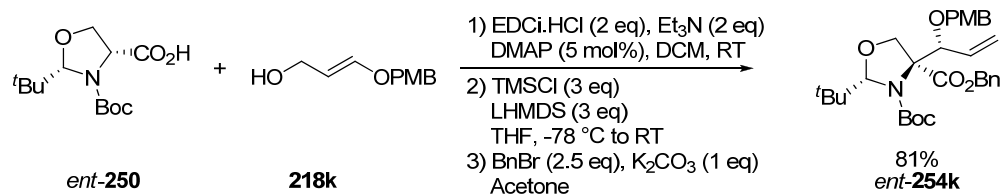
With the free hydroxyl synthesised it could be subjected to the optimised conditions obtained for the cross-metathesis reaction. Gratifyingly a more efficient cross-metathesis is seen to occur, with the reaction time cut by a third, and a vastly superior yield observed.



Scheme 100 - Cross-metathesis of allylic alcohol **290**

#### 4.2.3 Completion of the Synthesis of Mycestericin G

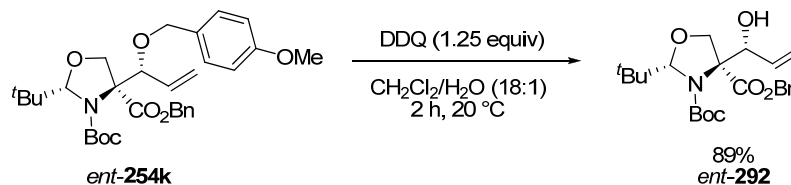
With a proficient cross-metathesis protocol established, a preparative scale synthesis of *ent*-**254k** was initiated.



Scheme 101 - Preparative scale rearrangement

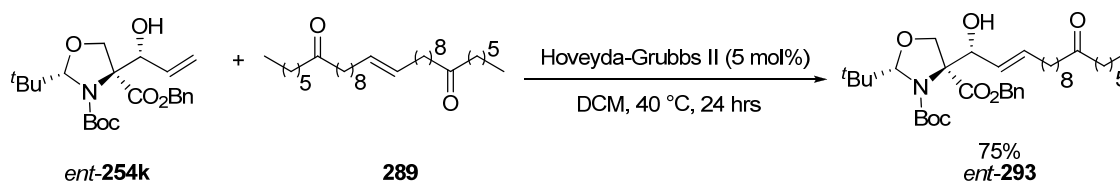
With gram quantities of *ent*-**254k** needed a streamlined procedure was performed with carbodiimide mediated coupling of **250** and **218k**, Ireland-Claisen rearrangement and

carboxyl benzoylation conducted on a 4 mmol scale without intermediate purification. In addition to shortening the laboratory procedure this served to increase the overall yield across the three synthetic steps.



**Scheme 102 - DDQ deprotection of PMB ether *ent*-254k**

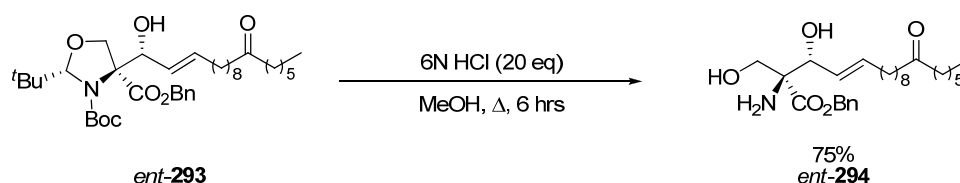
DDQ deprotection of the PMB group occurs in excellent yield. As seen in the synthesis of **290** (Scheme 99) *p*-anisaldehyde is present after initial workup. Removal by sodium borohydride reduction of aldehyde **290a** and subsequent flash chromatography results in a slight loss of yield to 74% (See 7.3 Compound Characterisation for further details), however, this additional layer of purification isn't required since the presence of the aldehyde bears no impact on the result of the ensuing cross-metathesis reaction.



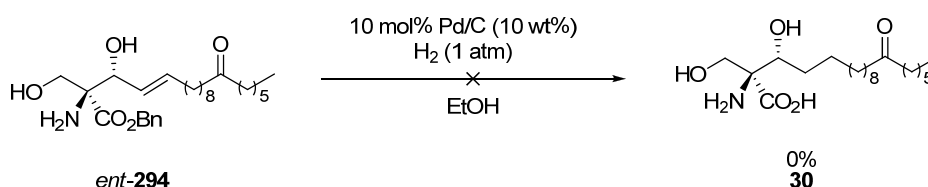
**Scheme 103 - Cross-metathesis towards the synthesis of mycestericin G**

The cross-metathesis proceeds well (Scheme 103), albeit with a slightly reduced yield when compared to the analogous methyl ester **291**. This continues the observations that steric bulk around the olefin serves to reduce the activity, and subsequent performance in the metathesis reaction.

With a successful cross-metathesis the two key structural features – the chiral head group and lipophilic tail – have been amalgamated with just two proposed steps remaining to synthesise mycestericin G. The first step, acidic hydrolysis of oxazolidine **ent-293**, formed amino diol **ent-294** in good yield (Scheme 104).

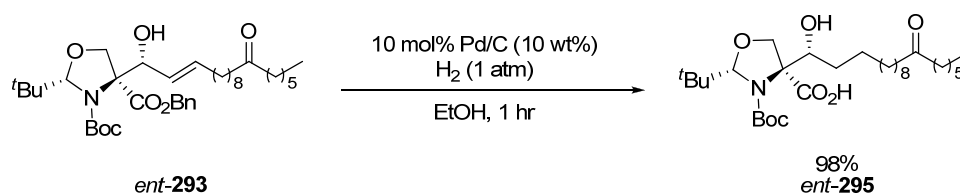
Scheme 104 - Acid hydrolysis of oxazolidine *ent*-292

Final hydrogenolysis of the benzyl ester and alkene however proved problematic. An initial attempt using 5 wt% palladium on carbon under an atmosphere of hydrogen failed to generate any sign of product. However, significant decomposition of the starting material was observed.

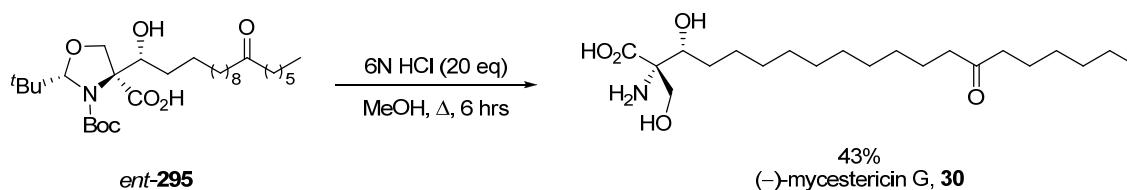
Scheme 105 - Attempted hydrogenation of amino diol *ent*-293

For the hydrogenation of a natural sample of mycestericin E, Fujita *et al.* utilised 200 wt% palladium on carbon to afford mycestericin G.<sup>50</sup> It can be reasoned that by using small catalytic quantities of palladium on carbon any desired hydrogenation is reacting at a far slower rate than decomposition of the starting material. By increasing the catalytic loading to near stoichiometric amounts it was hoped that the desired hydrogenation would occur more rapidly. Whilst trace amounts of mycestericin G could be discerned from the <sup>1</sup>H NMR spectrum, decomposition was still the dominating result from the reaction.

To circumnavigate this problem, the order of these transformations was reversed. Oxazolidine *ent*-293 was now subjected to hydrogenation allowing rapid reduction of the alkene, and cleavage of the benzyl ester in near quantitative yield (Scheme 106).

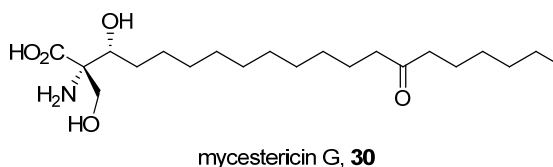
Scheme 106 - Hydrogenation of *ent*-292

Acid hydrolysis followed by basification of the subsequent hydrochloride salt afforded mycestericin G as a white powder (Scheme 107).



**Scheme 107 - Completion of mycestericin G synthesis**

Whilst all spectroscopic data was in accordance with previously published reports, the optical rotation of the synthetic compound was, however, opposite in sign, but of similar magnitude to that reported for the natural product (Figure 32).<sup>50</sup>



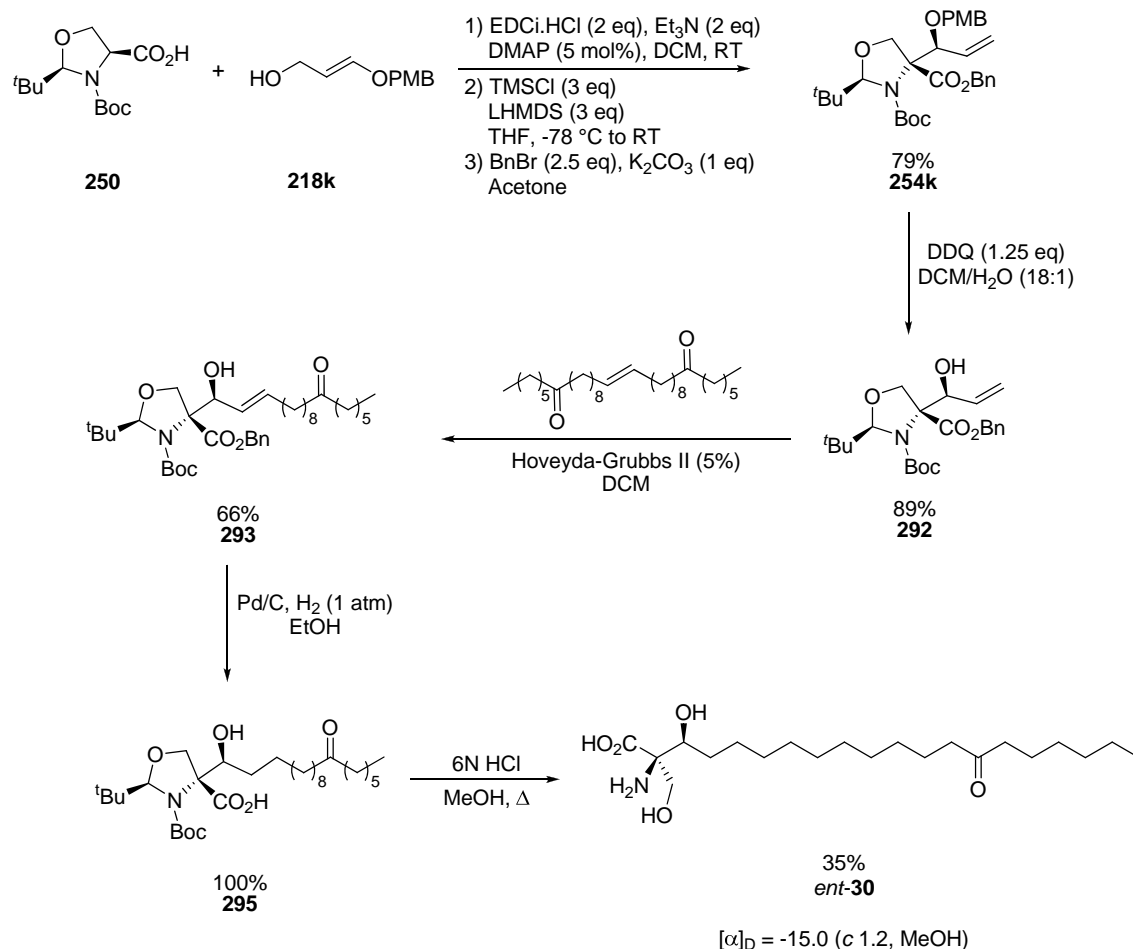
Natural Product:  $[\alpha]_D = -6.8$  (c 0.106, MeOH)  
 Synthetic Sample:  $[\alpha]_D = +13.3$  (c 0.3, MeOH)

**Figure 32 - Comparison of optical rotation between natural and synthetic mycestericin G**

To further understand and analyse this discrepancy the synthetic sequence was repeated starting from L-serine with the aim of synthesising the opposite enantiomer (Scheme 108).

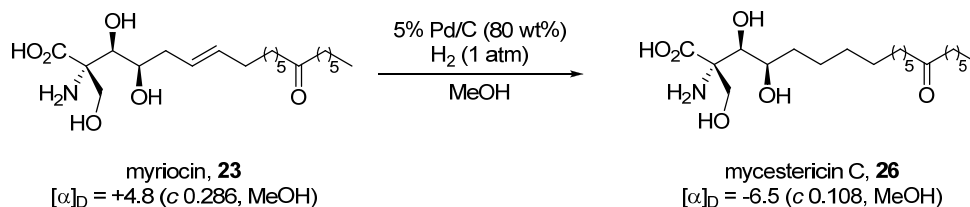
The spectroscopic data for *ent*-**30** was identical to that observed for the synthetic sequence derived from D-serine. However, the optical rotation was now not only similar in magnitude, but also of the same sign of rotation as the natural sample of mycestericin G.





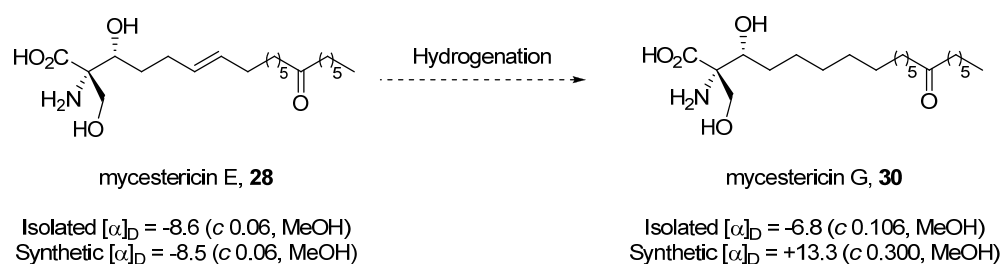
Scheme 108 - Synthesis of mycestericin G starting from L-Serine

This discrepancy can be explained by analysis of the literature of similar sphingosine natural products. Hydrogenation of myriocin **23**, forms dihydromyriocin (mycestericin C **26**). The key realisation in this transformation is that hydrogenation leads to a reversal in the sense of optical rotation; i.e., myriocin **23** is dextrorotatory, whilst mycestericin C **26** is levorotory (Scheme 109).

Scheme 109 - Hydrogenation of myriocin **23**, with inherent reversal in sense of optical rotation

Whilst the absolute configuration of mycestericin E **28** has been confirmed through its total synthesis, this is not the case for mycestericin G **30**, its saturated derivative.<sup>79</sup> The

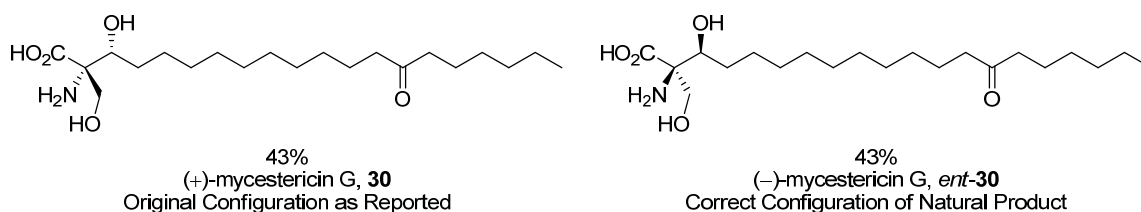
same report obtains mycestericin G **30** from synthetic mycestericin E **28**, and provides identical spectroscopic data when compared with a natural sample. However, no optical rotation data was reported for this synthetic mycestericin G. As a result, there is no unequivocal evidence that the configuration of the stereocentres in mycestericin E is the same as those in mycestericin G. Furthermore, the optical rotation observed for synthetically obtained mycestericin G in this body of work parallels the switch in sense of rotation between the unsaturated and saturated analogues.



**Scheme 110 - Hydrogenation of mycestericin E, with contrasting optical rotation between natural and synthetic mycestericin G**

Of particular interest when assessing this inconsistency with the optical rotations is the recent synthesis of mycestericin G by Kumagai and Shibasaki.<sup>82</sup> Synthesis of the originally reported structure resulted with an opposite sense of optical rotation to that in the original isolation paper ( $[\alpha]_D^{20} +12.8$  (*c* 0.05, MeOH)). This discrepancy was attributed to the poor solubility of mycestericin G in methanol.

These findings offer firm credence to a reassignment in the configuration of mycestericin G, such that it is enantiomeric to the original assignment (Figure 33).



**Figure 33 - (+)- and (-)-Mycestericin G: determination of configuration**

### 4.3 Total Synthesis of Threonine Analogue of Mycestericin G

Drug discovery has long used the process of structure-activity relationships to develop a lead compound into a safer, and more effective clinical agent. Bioisosterism and other structural changes have regularly been used to accomplish the desired enhancement in efficacy, or to reduce levels of toxicity.<sup>243</sup>

With the successful synthesis and reassignment of mycestericin G, the heteroproline rearrangements conducted in section 2.4.3 Rearrangement of Heteroproline Allyl Esters offer an efficient route into (2*S*,3*R*)-2-amino-3-hydroxy-2-((*R*)-1-hydroxyethyl)-14-oxoicosanoic acid **296**; an analogue of mycestericin G with a chiral head group derived from threonine, rather than serine. It can be envisaged that the same synthetic route will be applicable for the mycestericin G analogue.

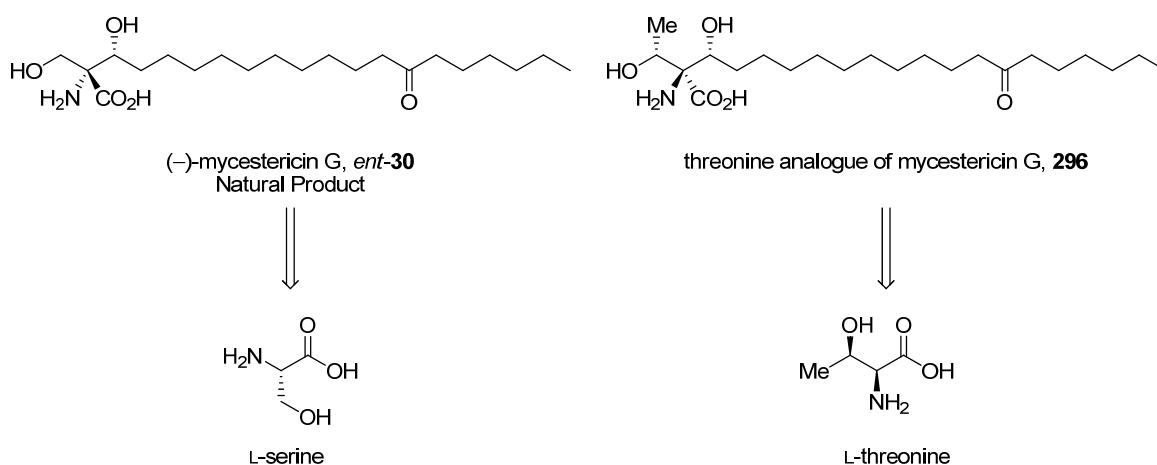
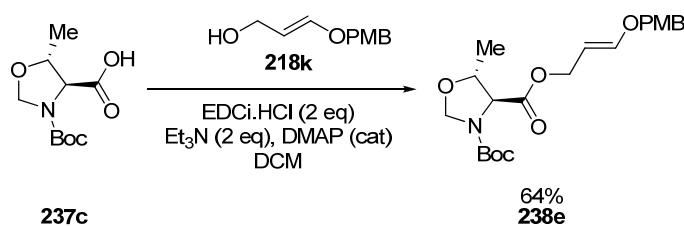


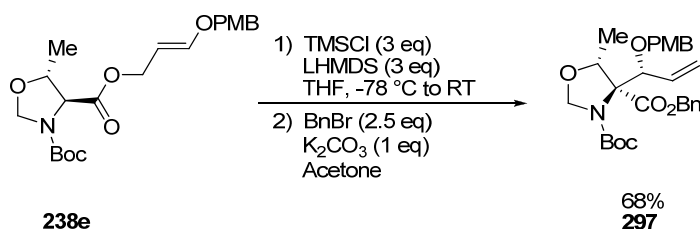
Figure 34 - A potential analogue of mycestericin G

*p*-Methoxybenzyl enol ether **218k** was coupled with the 5-methyloxazolidine **237c** in good yield, to afford the substrate required for the key Ireland-Claisen rearrangement (Scheme 111).



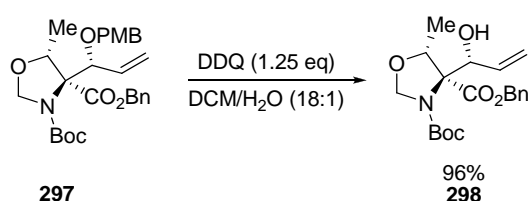
**Scheme 111 - Carbodiimide promoted esterification of 5-methyloxazolidine**

An efficient rearrangement was seen to occur under the standard conditions used for these oxazolidine class of compounds (Scheme 112). With a single diastereomer observed, in good yield, the contiguous stereocentres of the chiral head group are now installed.



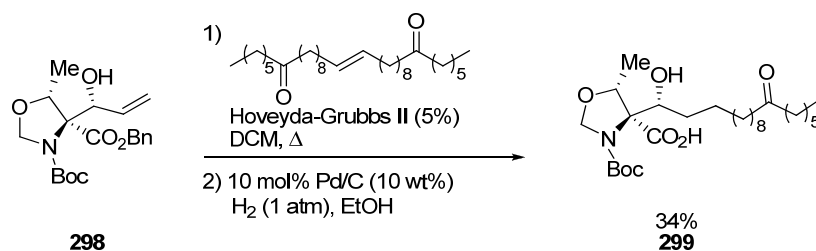
**Scheme 112 - Rearrangement of *p*-methoxybenzyl oxazolidine ester**

DDQ deprotection of the PMB group occurs in excellent yield, and, gratifyingly, separation of the anisaldehyde from the desired product is achievable by flash chromatography (Scheme 113).



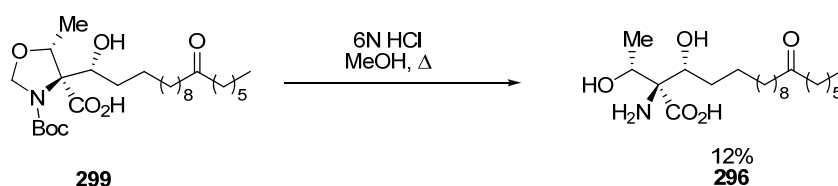
**Scheme 113 - DDQ deprotection**

The cross-metathesis suffers from a lower yield when compared to the 2-*t*-butyl oxazolidine cross-metathesis. As has been observed across the range of substrates used in this cross-metathesis, any increase in steric congestion appears to severely hinder the reaction. In this case, the proximity of the methyl group on the oxazolidine must be hindering the reaction. When followed by a hydrogenation over palladium on carbon, a yield of 34% is obtained over the two steps (Scheme 114).



Scheme 114 - Cross-metathesis and hydrogenation

Acid hydrolysis completes the synthesis, albeit, in a low yield. The poor yield can be explained due to partial solubility of the amino acid in water. The nature of the work up involved basification with aqueous sodium hydroxide, concentration *in vacuo* and then dissolution of the residue in water, from which the desired product precipitated as a white solid. In the case of mycestericin G, a significant quantity precipitates. The threonine analogue was observed to have a higher affinity to the water, and as a result, a decrease in yield was obtained.



Scheme 115 - Completion of the synthesis of the threonine analogue of mycestericin G, 296

#### 4.4 Conclusion

Both enantiomers of mycestericin G have been synthesised in a concise 10 step synthesis starting from the readily available serine methyl ester hydrochloride salt. The natural product (–)-mycestericin G (*ent*-**30**) first isolated from *Mycelia sterilia* was obtained in an 9.7% overall yield after its enantiomer was first synthesised in 13.5% overall yield. Key steps in the synthesis were the Ireland-Claisen rearrangement (the methodology for which has been previously discussed in Chapter 3), and the cross-metathesis. These steps allowed the synthesis of the chiral head group, and it's coupling to the lipophilic tail seen in the natural product.

Synthesis of both enantiomers of the natural product, allowed a revision of the stereochemistry to be made. Confidence in this reassignment is augmented by the XRD

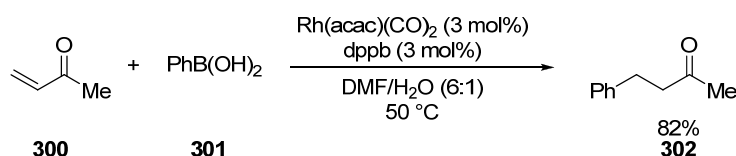
analysis obtained from a rearrangement product (Figure 24), which verified the predicted outcome of the Ireland-Claisen rearrangement, along with the optical rotation for mycestericin G seen by Kumagai and Shibasaki.

The synthetic route used in the synthesis has been shown to be applicable not only to mycestericin G, but also allows for synthetic derivations to be made, of which the threonine analogue **296** has successfully been synthesised over 9 linear steps. Whilst increased steric interactions lower the yield of the cross-metathesis, and solubility issues affect the acid hydrolysis a quick, and efficient synthesis is still obtained.

## 5. CHIRAL DIENE LIGANDS IN CONJUGATE ADDITIONS

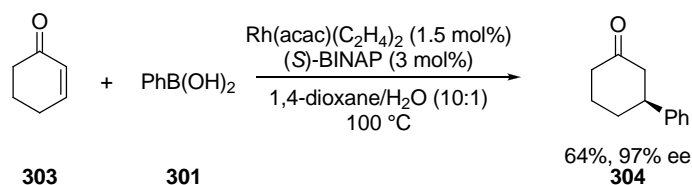
### 5.1 Introduction

Transition metal-catalysed conjugate addition of organometallic reagents to activated alkenes has become a powerful method in organic synthesis.<sup>244</sup> Part of the power of this chemistry stems from the ability to tune reactivity with countless ligand and metal combinations.<sup>245</sup> In 1997 Miyaura *et al.* published the first report on the rhodium-catalysed conjugate addition of both aryl and alkenyl boronic acids to methyl vinyl ketone (Scheme 116).<sup>246</sup>



**Scheme 116 - Rhodium-catalysed conjugate addition of phenyl boronic acid and methyl vinyl ketone**

In collaboration with Hiyashi *et al.*, the first asymmetric rhodium-catalysed conjugate addition was observed with the addition of a range of electron-donating and electron-withdrawing aryl boronic acids to 2-cyclohexenone (Scheme 117).<sup>247</sup> The excellent yields and enantioselectivities observed in this reaction have become the benchmark for rhodium-catalysed conjugate addition.<sup>248</sup>

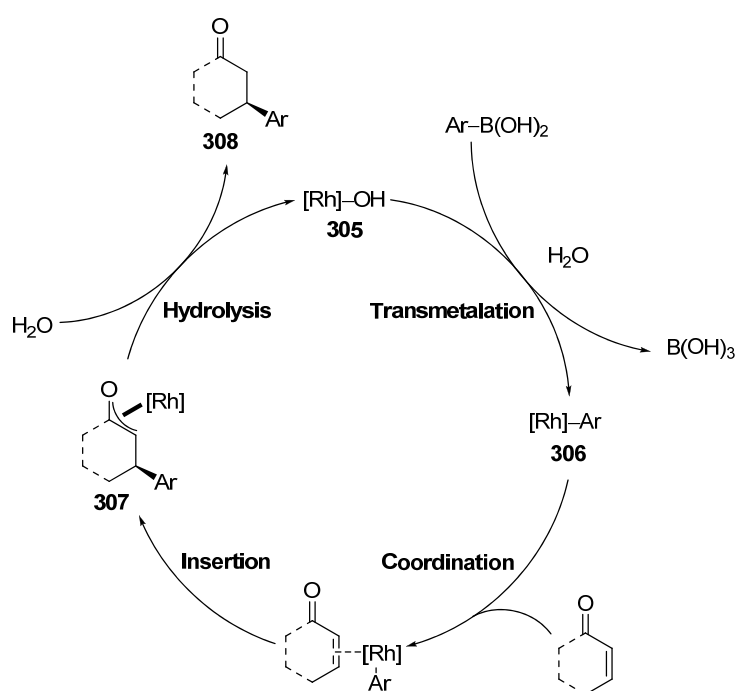


**Scheme 117 - First enantioselective rhodium-catalysed conjugate addition**

#### 5.1.1 Mechanism of Rhodium-Catalysed Conjugate Additions

The discovery by Miyaura *et al.* that the addition of base accelerated the conjugate addition to  $\alpha,\beta$ -unsaturated amides contributed to the discussion that the active precursor is a hydroxy-rhodium species **305**.<sup>249</sup> Such a species was confirmed by Hayashi *et al.* in their mechanistic study with  $^{31}\text{P}$  NMR spectra.<sup>250</sup>

The first step of the mechanism involves the formation of the active rhodium-hydroxyl precursor **305** by loss of ligands (such as acac or Cl). This reactive species then undergoes transmetalation with the desired organoboron reagent to form the aryl-rhodium species **306** (Scheme 118). It is usual to use an excess of organoboron reagent due to a competitive protodeboronation pathway. Coordination and insertion of the unsaturated carbon-carbon double bond leads to the  $\eta^3$ -oxa- $\pi$ -allylrhodium complex **307**. Enantioselectivity in the product is obtained from the facial selectivity of the chiral ligand. Hydrolysis of the rhodium-enolate with water regenerates the active catalyst along with the conjugate-addition product **308**.



**Scheme 118 - The mechanism of rhodium-catalysed conjugate addition**

Rhodium-catalysed conjugate addition reactions aren't confined solely to organoboron reagents; many other organometallics participate in transmetalation to rhodium. Whilst other organometallic donors can offer different advantages and reaction pathways, they will not be discussed further here, but can be found in a review by Frost *et al.*<sup>251</sup>

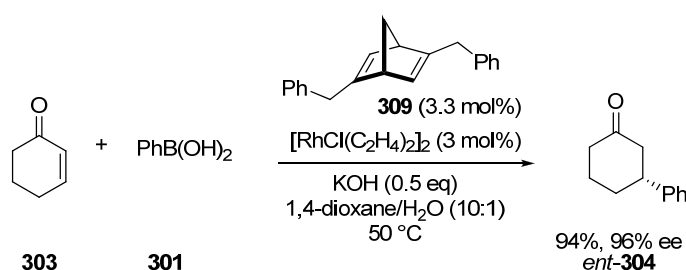
### 5.1.2 Chiral Diene Ligands in Rhodium-Catalysed Conjugate Additions

Since these reports, the application and range of organoboron reagents has grown exponentially. In particular, the development of chiral diene ligands have found this



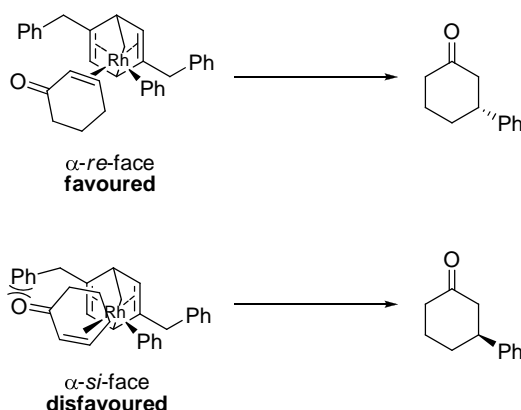
class of ligand to be superior to many other types of chiral ligands, such as bisphosphines. Not only can they show enhanced catalytic activity, but also enantioselectivity, particularly in rhodium-catalysed asymmetric transformations.<sup>252</sup>

Achiral chelating ligands such as 1,5-cyclooctadiene (cod) and norbornadiene (nbd) were known to be stable ligands in transition metal complexes<sup>253</sup>, however, it wasn't until 2003 when a chiral diene ligand was developed by Hayashi *et al.*<sup>254</sup> Derived from norbornadiene in 9 steps, (*R,R*)-Bn-nbd **309** was successfully utilised in the conjugate addition of arylboronic acids to  $\alpha,\beta$ -unsaturated ketones and esters with high yields and excellent enantioselectivities (Scheme 119).



Scheme 119 - First use of a chiral diene ligand in a rhodium-catalysed conjugate addition

The **309**-rhodium complex is able to recognise the enantioface of the enone due to steric repulsion of the benzyl group on the diene, and the carbonyl moiety. The implication of this is the  $\alpha$ -*re*-face being favoured over the  $\alpha$ -*si*-face for both cyclic and linear enones (Scheme 120).



Scheme 120 - Enantioselectivity in a rhodium-catalysed conjugate addition

Since this first publication, bicyclic diene frameworks have been further developed.<sup>252</sup> Noteworthy amongst these is Carreira's diene **311**, readily derived from (–)-carvone in a seven step synthesis (Figure 35).<sup>255-256</sup>

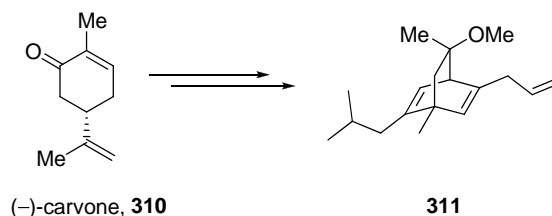


Figure 35 - Carreira's diene, derived from (–)-carvone

Despite such bicyclic ligands offering excellent substrate scope and high enantioselectivities, there is a need to increase ligand availability.<sup>257</sup> To this end simple chiral dienes have been reported by Du *et al.*, and Trost *et al.* which lack the rigidity of the bicyclic ligands.<sup>257-258</sup>

Du described a simple chain diene **312** that achieved moderate enantioselectivities as a starting point for a new and practical direction in the design of future chiral diene ligands. Further modifications by Du saw ligand **313** achieve higher selectivities, up to 95% ee.<sup>259</sup> Whilst seeing improvements in enantioselectivity, this new ligand requires a longer, six step synthesis from 1,5-hexadiene.

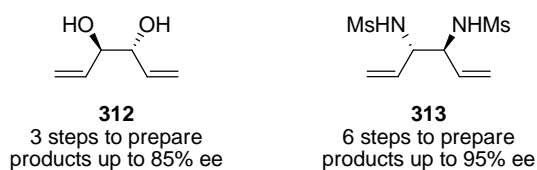
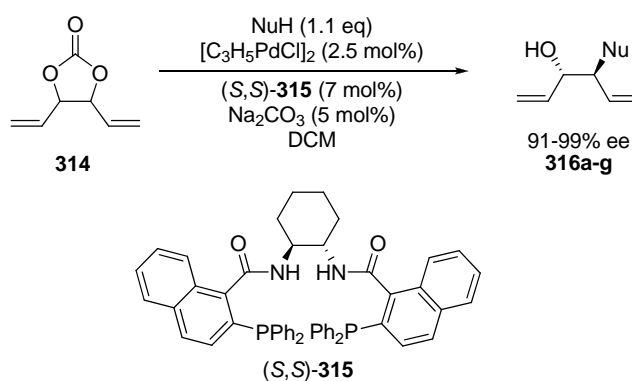


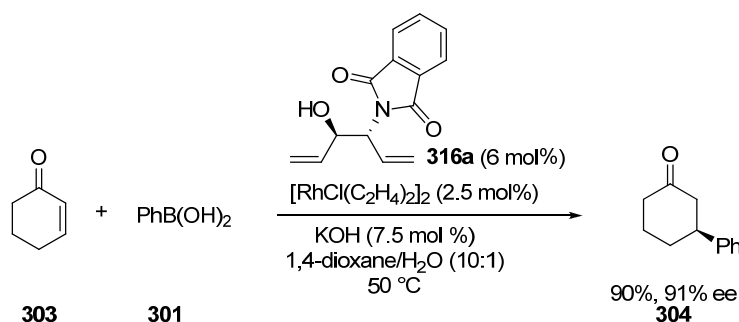
Figure 36 - Du's chiral chain diene ligand development

Trost's aims were specifically to create “a more convenient synthetic approach towards chiral dienes for use in transition metal catalysis”.<sup>257</sup> Furthermore he felt it was desirable to produce a structurally diverse library of ligands from a common intermediate. By using palladium-catalysed asymmetric allylic alkylation (Pd-AAA) on *meso*- and *d,l*-divinylethylene carbonate with a variety of nucleophiles, a series of potential ligands were synthesised (Scheme 121).



Scheme 121 - Synthesis of chiral diene ligands via a Pd-AAA

Ligand **316a** prepared from the Pd-AAA using phthalimide gave superior enantioselectivity and yield over the other ligands synthesised, and was subsequently utilised to show the general applicability of this chiral diene ligand (Scheme 122).



Scheme 122 - Application of Trost's chiral diene ligand in Rh-catalysed conjugate addition

### 5.1.3 Hybrid Olefin Ligands in Rhodium-Catalysed Conjugate Additions

In the attempt to achieve ever higher catalytic activity and selectivity phosphorous/olefin<sup>260-262</sup> and nitrogen/olefin<sup>263</sup> hybrid ligands have been developed, and successfully utilised in many transition-metal-catalysed asymmetric reactions. However, recent advances have seen a rise in interest in chiral sulphur-containing ligands, due to their availability, high stability, metal affinity, and in particular, *S*-stereogenic control.<sup>264</sup> The use of chiral sulphur-olefin hybrid ligands in rhodium-catalysed conjugate additions was simultaneously reported by Knochel,<sup>265</sup> Xu,<sup>266-267</sup> and Du,<sup>268</sup> with promising activity and selectivity observed (see ligands **317**, **318**, and **319** respectively, Figure 37).

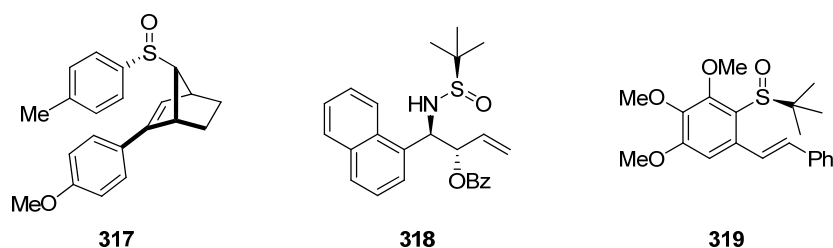
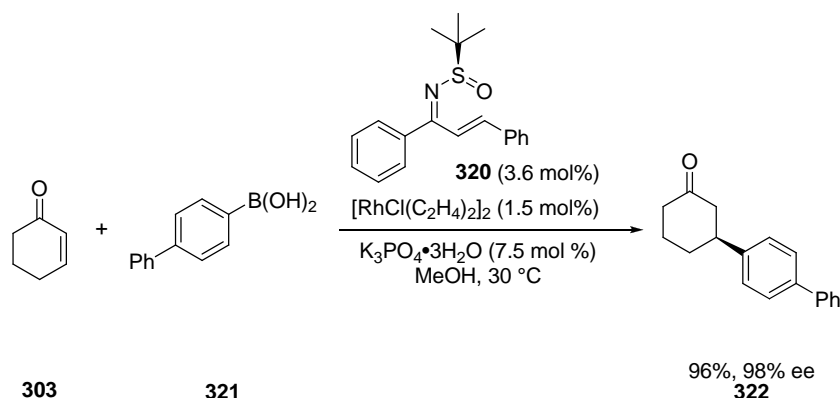


Figure 37 - Recent chiral sulphur/olefin ligand development

Du *et al.* have developed a series of chiral *N-tert*-butanesulfinyl  $\alpha,\beta$ -unsaturated ketimines through a one step condensation of  $\alpha,\beta$ -unsaturated ketones with *tert*-butanesulfinamide.<sup>269</sup> Ligand **320**, obtained from chalcone showed both the highest reactivity and enantioselectivity in a rhodium-catalysed conjugate addition (Scheme 123).



Scheme 123 - Rhodium-catalysed conjugate addition using a sulphur/olefin ligand

The diverse range of ligand structures this one step procedure allows, along with the high yields and enantioselectivities shown make this class of ligands highly attractive to a variety of transition-metal-catalysed asymmetric reactions.

## 5.2 Rhodium-Catalysed Conjugate Addition

### 5.2.1 Ligand Synthesis

With such interest in new ligand systems for rhodium-catalysed conjugate addition reactions, it was felt that the rearrangement products seen in Chapter 3 can be transformed into chiral diene ligands with just a few functional group interconversions. It was envisaged that reduction of the methyl ester to an aldehyde, followed by a Wittig

reaction would furnish the desired diene in a quick synthetic sequence (Figure 38). Unfortunately, as previously discussed, selective reduction to the aldehyde is not amenable, therefore it is necessary to proceed *via* the primary alcohol with subsequent oxidation to the aldehyde.

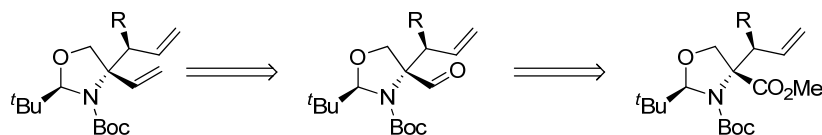
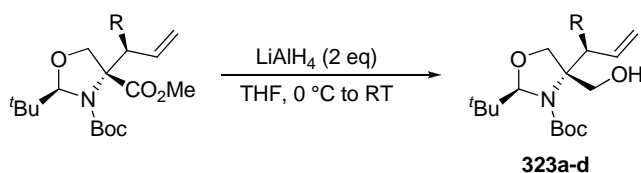


Figure 38 - Chiral diene ligands from rearrangement products

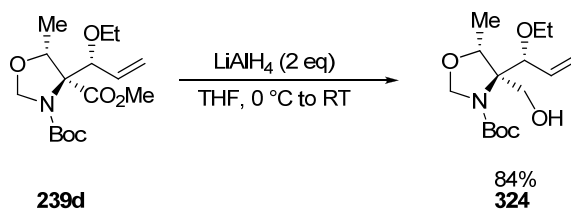
A selection of rearrangement products were chosen to allow a broad range of ligands to be screened in the rhodium-catalysed conjugate addition (Table 33).

Table 33 - Lithium aluminium hydride reduction of *tert*-butyloxazolidine methyl esters



Entry	Substrate	R	Product	Yield
1	<b>252b</b>	OEt	<b>323a</b>	100%
2	<b>252g</b>	OPMP	<b>323b</b>	89%
3	<b>266a</b>	H	<b>323c</b>	100%
4	<b>266b</b>	Me	<b>323d</b>	98%

In addition to these four examples based on the *tert*-butyloxazolidine core, a single example based on the threonine-derived oxazolidine was desired to allow a comparison in the conjugate addition. As was seen with the *tert*-butyloxazolidine reductions, an excellent yield was obtained (Scheme 124).



Scheme 124 - Lithium aluminium hydride reduction of methyloxazolidine methyl ester

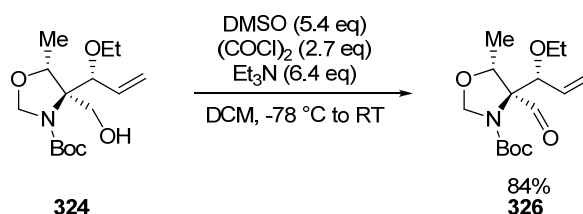
Pleasingly, subsequent Swern oxidation proceeded with very good yields across all four *tert*-butyloxazolidine substrates (Table 34). It should be noted, that neither the reduction, nor oxidation steps required purification by flash chromatography, making these operationally simple reactions to perform.

**Table 34 - Swern oxidation of *tert*-butyloxazolidine primary alcohols**

$\text{323a-d} \xrightarrow[\text{DCM, -78 } ^\circ\text{C to RT}]{\text{DMSO (5.4 eq), (COCl)}_2 \text{ (2.7 eq), Et}_3\text{N (6.4 eq)}} \text{325a-d}$

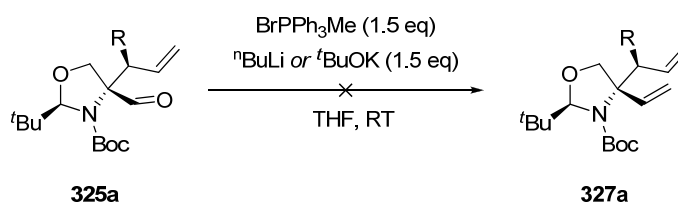
Entry	Substrate	R	Product	Yield
1	<b>323a</b>	OEt	<b>325a</b>	78%
2	<b>323b</b>	OPMP	<b>325b</b>	80%
3	<b>323c</b>	H	<b>325c</b>	75%
4	<b>323d</b>	Me	<b>325d</b>	82%

The threonine derived methyloxazolidine also oxidised cleanly to obtain the desired aldehyde with an excellent yield (Scheme 125).



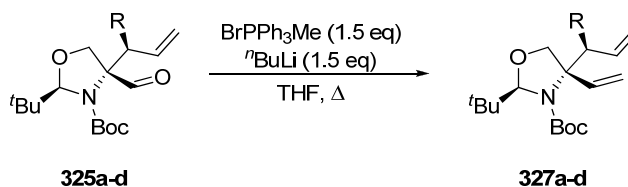
**Scheme 125 - Swern oxidation of methyloxazolidine primary alcohol**

The final step of the synthesis is to install the olefin by a Wittig reaction. Initial efforts focused on the ethoxy aldehyde **325a**, with a range of conditions attempted before successfully obtaining any sign of the desired diene. Use of either *n*BuLi or *t*BuOK at room temperature failed to show any sign of conversion (Scheme 126).



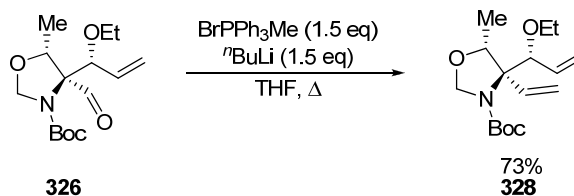
Scheme 126 - Attempted Wittig reaction

However, on heating to reflux, an 87% yield was gratifyingly obtained. These conditions allowed a successful reaction for all *tert*-butyloxazolidine aldehydes with high yields for all four substrates (Table 35).

Table 35 - Wittig reaction of *tert*-butyloxazolidine aldehydes

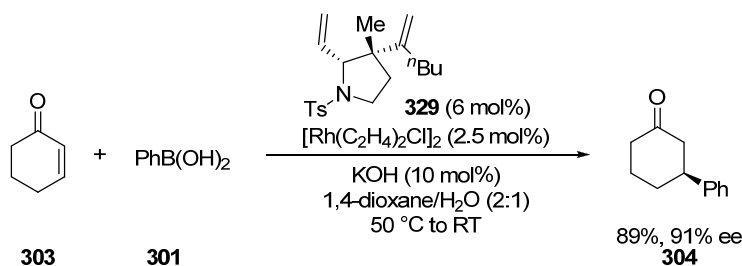
Entry	Substrate	R	Product	Yield
1	<b>325a</b>	OEt	<b>327a</b>	87%
2	<b>325b</b>	OPMP	<b>327b</b>	74%
3	<b>325c</b>	H	<b>327c</b>	78%
4	<b>325d</b>	Me	<b>327d</b>	69%

Methyloxazolidine **326** was also amenable to the Wittig reaction, with the desired diene **328** formed in 73% yield (Scheme 127).

Scheme 127 - Wittig reaction of methyloxazolidine aldehyde **326**

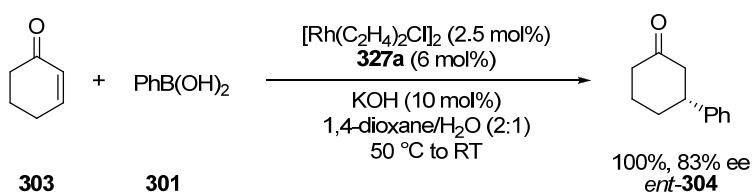
### 5.2.2 Ligand Screening

With a range of chiral diene ligands now synthesised, the rhodium-catalysed conjugate addition can be attempted. Yu *et al.* had recently reported the use of an  $\alpha,\beta$ -divinyl tetrahydropyrrole **329** as a chiral chain diene ligand (Scheme 128), and these optimised conditions were used as a starting point in this investigation.<sup>270</sup>



Scheme 128 - Yu's  $\alpha,\beta$ -divinyl tetrahydropyrrole in a rhodium-catalysed conjugate addition

An initial reaction using ethoxyallyl ligand **327a** (Scheme 129) showed, by TLC, that some starting material was still present after 18 hours. The reaction was subsequently concentrated *in vacuo* where the crude <sup>1</sup>H NMR showed no sign of starting material. Indeed, TLC analysis now also showed that there was no starting material present. After purification by flash chromatography, a quantitative yield was obtained with an 83% ee. From this observation, it appeared that any residual starting material was being consumed whilst in the rotary evaporator.



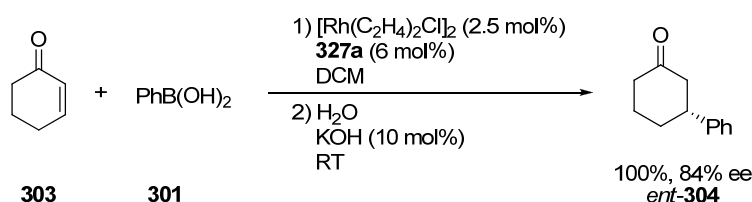
Scheme 129 - Initial conjugated addition of phenylboronic acid to 2-cyclohexenone, using **327a**

To probe this interesting observation further, two additional reactions were conducted. Firstly, an aqueous workup was conducted on the reaction mixture in place of rotary evaporation; whilst the second saw the reaction mixture immediately transferred to the rotary evaporator on addition of 2-cyclohexenone **303**. After 18 hours and an aqueous workup, there was still starting material present by TLC. An isolated yield of 64% was obtained, along with a slightly improved ee of 87%. Meanwhile, the second test reaction



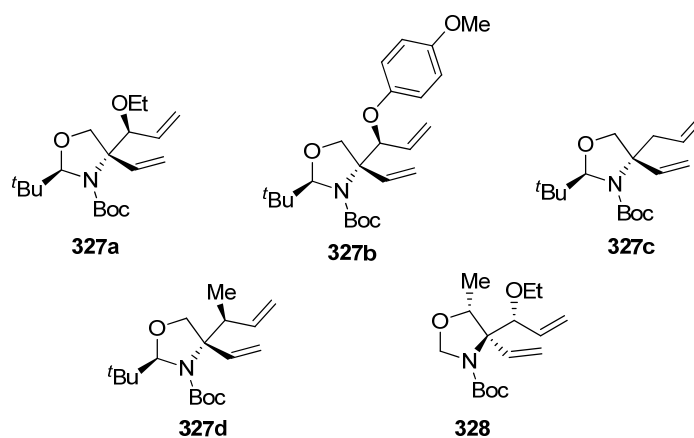
saw a near quantitative yield of 98% returned, with a near identical enantioselectivity seen to the initial reaction (that is 84% ee). These results confirm the belief that the reaction is being driven to completion whilst under rotary evaporation. It is worth noting, that on conducting these experiments on the rotary evaporator, if less water was used relative to 1,4-dioxane, then the reactions could fail to go to completion.

To explore this effect further a solvent swap was conducted. The initial coordination of the rhodium and chiral ligand was conducted in dichloromethane, before removal under reduced pressure, and then addition of water, potassium hydroxide and 2-cyclohexenone. An aqueous work up followed, to avoid any further reaction *in vacuo*. Whilst a quantitative conversion, and isolated yield were obtained, there was no improvement in enantioselectivity (Scheme 130).



**Scheme 130 - Solvent swap investigation into the effect of water on the conjugated addition**

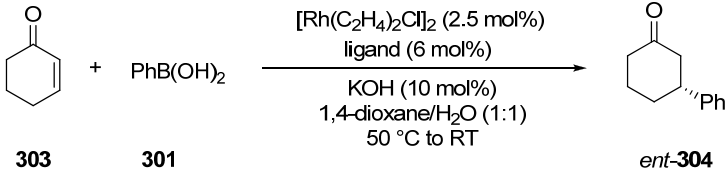
With two conditions acquired that allows complete consumption of the starting material, the decision was made to use the more operationally simple procedure, and to immediately place the reaction mixture on the rotary evaporator. With the experimental conditions now chosen, ligands **327a-d**, and **328** (Figure 39) were compared in the conjugate addition of phenylboronic acid to 2-cyclohexenone.



**Figure 39 - Chiral diene ligands**

It can be seen that both the ethoxyallyl, and allyl substituted ligands (**327a** and **327c** respectively) proceed in quantitative yield, with good enantioselectivity (Table 36, entries 1 and 3). There is a slight drop off in both activity and enantioselectivity with *para*-methoxyphenyl ligand **327b** (entry 2), falling to 49% yield and 68% ee for methyl ligand **327d** (entry 4). Threonine derived ligand **328** fails to offer much conversion, with a poor yield of 13%, and a moderate 51% ee (entry 5).

Table 36 - Chiral diene ligand screening

			
Entry	Ligand	Yield (%)	ee (%) <sup>[a]</sup>
1	<b>327a</b>	100	83
2	<b>327b</b>	86	72
3	<b>327c</b>	100	87
4	<b>327d</b>	49	68
5	<b>328</b>	13	51 <sup>[b]</sup>

<sup>[a]</sup> ee was determined by HPLC (Chiralpak AD column) <sup>[b]</sup> Opposite enantiomer (i.e. **304**) obtained

### 5.2.3 Ligand Development

With allyl ligand **327c** showing the highest enantioselectivity, along with a quantitative yield, further alkyl based ligands were desired to investigate effects of substitution on the olefin itself. With new ligands **327e** and **327f** identified, a route was required for their synthesis.

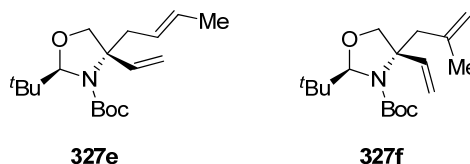
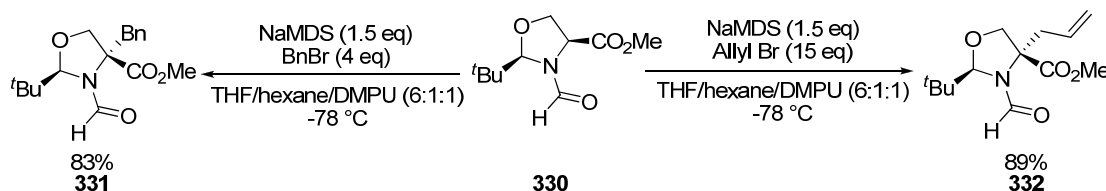


Figure 40 - Additional chiral diene ligands

Alkylation of oxazolidine **249** was anticipated to provide the quickest synthetic access to these desired ligands. It was also envisaged that alkylation with allyl bromide would provide an alternative method for the synthesis of ligand **327c**.



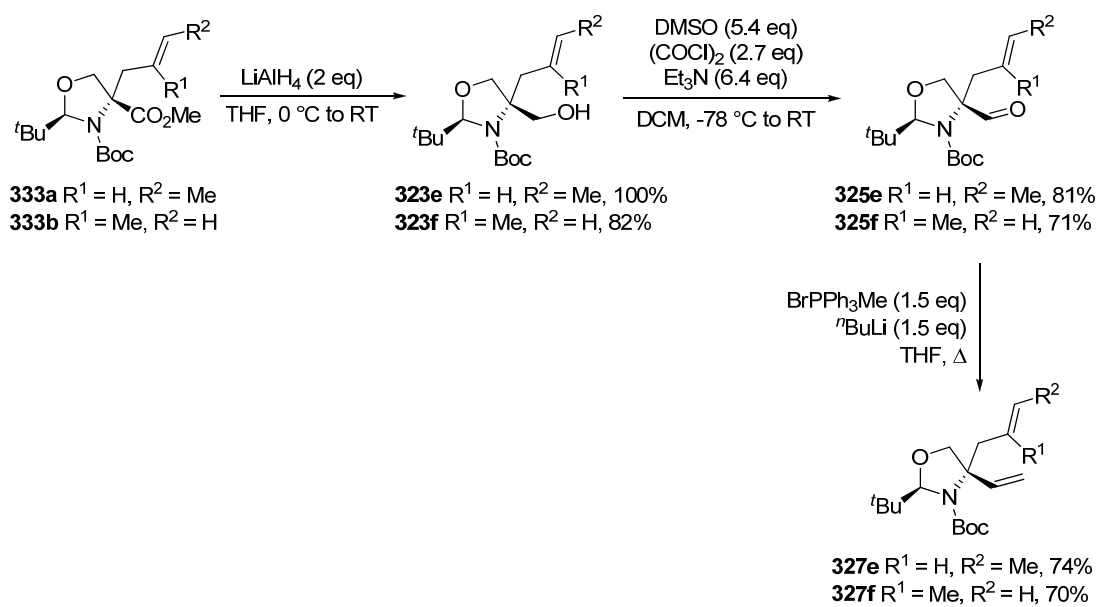
**Scheme 131 - Alkylation of formyl oxazolidine 329**

Following a procedure by Colombo and Giacomo, which reported the alkylation of analogous formyl oxazolidine **330** with a large excess of alkyl halide (Scheme 131),<sup>198</sup> a selection of conditions were attempted using allyl bromide as a test electrophile. This showed a significant drop in yield when 4 equivalents of alkylating agent was used, compared to the 15 equivalents used by Colombo *et al.* However, reducing the number of equivalents to 10, an increase in yield to 81% was observed. Further changes made were to use LHMDs, and the removal of additional additives and co-solvents from the reaction. With these modifications in place a range of electrophiles were reacted with the enolate of oxazolidine **249** (Table 37). With 3-chloro-2-methylprop-1-ene failing to react, the iodoalkane was synthesised using a Finkelstein reaction.<sup>271</sup>

**Table 37 - Alkylation of oxazolidine 249**

Entry	E	R <sup>1</sup>	R <sup>2</sup>	x (eq)	Product	Yield (%)
1		H	H	4	<b>266a</b>	50
2		H	H	10	<b>266a</b>	81
3		H	H	15	<b>266a</b>	75
4		H	Me	10	<b>333a</b>	90
5		Me	H	10	<b>333b</b>	0
6		Me	H	10	<b>333b</b>	76

With alkylation now successful, addition products **333a-b** were subjected to the same functional group interconversions to obtain the desired chiral diene. Both reduction and oxidation steps proceeded smoothly and, without the requirement for column chromatography, allow facile access to aldehydes **327e-f**. The Wittig reaction proceeds in similar high yields as seen previously (Scheme 132).



**Scheme 132 - Synthetic steps towards chiral diene ligands**

With these substituted allyl ligands now synthesised. A comparison could be made against allyl ligand **327c** (Table 38, entry 1). Unfortunately, whilst diene ligand **327e** shows high enantioselectivity, it fails to improve upon that seen for **327c**. Furthermore, the additional substitution appears to limit reactivity, and a moderate yield of 40% is obtained (entry 2). Whilst not appearing to affect the reactivity as severely as diene **327e**, **327f** suffers a large decrease in enantioselectivity (entry 3).

Table 38 - Additional ligand screening

Entry	Ligand	Yield (%)	ee (%) <sup>[a]</sup>
1	327c	100	87
2	327e	40	84
3	327f	78	49

<sup>[a]</sup> ee was determined by HPLC (Chiralpak AD column)

### 5.2.4 Reaction Optimisation

With allyl ligand **327c** showing excellent enantioselectivity and yields after the ligand screening, further optimisation was conducted to ensure maximum enantioselectivity was being achieved (Table 39).

Table 39 - Reaction optimisation using allyl ligand **327c**

Entry	Temp	Time	Yield (%)	ee (%) <sup>[c]</sup>
1	50 °C to RT	1 min <sup>[a]</sup>	100	87
2	RT	1 min <sup>[a]</sup>	100	88
3	RT	2.5 hrs <sup>[b]</sup>	17	83
4	RT	24 hrs <sup>[b]</sup>	16	88
5	RT to 100 °C	2.5 hrs <sup>[b]</sup>	97	82

<sup>[a]</sup> Reaction transferred immediately to rotary evaporator on addition of **303**. <sup>[b]</sup> Reaction subjected to aqueous work-up <sup>[c]</sup> ee was determined by HPLC (Chiralpak AD column)

Most literature reports specify 50 °C as the optimum temperature to allow catalyst/ligand exchange. However, it can be seen that this can be done at room temperature with no loss in yield, and a slight increase in enantioselectivity (entries 1 &

2). Moreover, this removes the need to allow the reaction mixture to cool prior to addition of 2-cyclohexenone **303**. It can be seen that under normal reaction conditions (that is, stirring under an inert atmosphere), the reactions proceed sluggishly, even with extended reaction times (entries 3 and 4). However, on heating to 100 °C, it is driven to completion, and a near quantitative yield is obtained (entry 5). Unfortunately, the enantioselectivity is lower than that seen under rotary evaporation.

### 5.2.5 Reaction Scope

With a suitable chiral diene ligand and optimised set of reaction conditions identified, the scope of the conjugate addition could be investigated.

Generally excellent yields are seen for all substrates, with 4-acetylphenyl **333d** the sole exception with a poor yield of 24% (entry 5). The highest enantioselectivities are seen for the smallest substituents (entries 1 and 2), with the largest substituent, 1-naphthalenyl **333c**, showing a decrease in selectivity to 73% ee. Whilst the 4-chlorophenyl **333e** (entry 6) is afforded in excellent yield, it was not possible to obtain an accurate ee, due to the lack of resolution of the enantiomeric peaks by chiral HPLC.

**Table 40 - Scope of rhodium-catalysed conjugate addition**

Reaction scheme: 2-cyclohexenone (**303**) +  $\text{R-C}_6\text{H}_4\text{-B(OH)}_2$   $\xrightarrow[\text{1,4-dioxane/H}_2\text{O (1:1), RT}]{\text{[Rh(C}_2\text{H}_4)_2\text{Cl]}_2 \text{ (2.5 mol\%), KOH (10 mol\%), 327c (6 mol\%)}}$   $\text{ent-304, 333a-e}$

Entry	R	Product	Yield (%)	ee (%) <sup>[a]</sup>
1	H	<i>ent</i> - <b>304</b>	100	88
2	4-F	<b>334a</b>	95	91
3	4-OMe	<b>334b</b>	93	84
4	1-Naphth	<b>334c</b>	100	73
5	4-Acetyl	<b>334d</b>	24	79
6	4-Cl	<b>334e</b>	87	ND <sup>[b]</sup>

<sup>[a]</sup> ee was determined by HPLC (Chiralpak AD, OD-H, or OJ column) <sup>[b]</sup> Unable to effect resolution of enantiomeric peaks by chiral HPLC

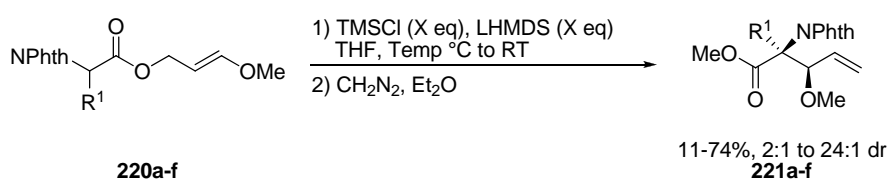
### 5.3 Conclusions

This short investigation into rhodium-catalysed conjugate addition reactions has afforded a promising series of results. A series of chiral diene ligands have been synthesised based on both *tert*-butyloxazolidine and methyloxazolidine cores. These have demonstrated excellent enantioselectivity in rhodium-catalysed conjugate addition reactions, with *tert*-butyloxazolidine allyl ligand **327c** showing the highest enantioselectivities. A series of aryl boronic acids have been successfully employed in the conjugate addition to 2-cyclohexenone, showing this catalyst-ligand system to be general, with good to excellent enantioselectivities obtained.

## 6. CONCLUSIONS & FUTURE WORK

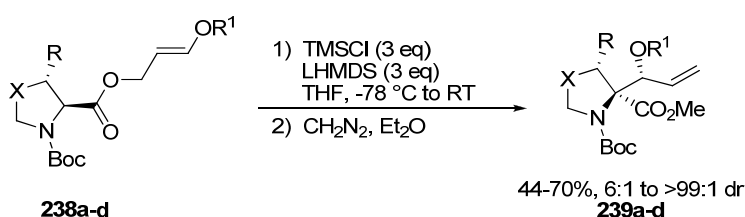
### 6.1 Conclusions

Efforts towards the synthesis of  $\alpha$ -quaternary centres in  $\beta$ -alkoxy- $\alpha$ -amino acids through an Ireland-Claisen rearrangement have shown the considerable effects that substituent size has on the reaction. Nonetheless, a series of individual optimisations allowed formation of the desired  $\beta$ -alkoxy- $\alpha$ -amino acids in 11-74% yield, and with diastereomeric ratios of 2:1 up to 24:1.



**Scheme 133 - Synthesis of  $\alpha$ -quaternary  $\beta$ -methoxy- $\alpha$ -amino acids**

In the course of this study, attempts had failed to protect serine with phthalic anhydride. However, using the rearrangement of proline methoxyallyl ester **233** as inspiration, serine, threonine and cysteine were protected using formaldehyde to form a series of heteroprolines. These all underwent rearrangement to give good to excellent diastereoselectivities, with moderate to good yields.



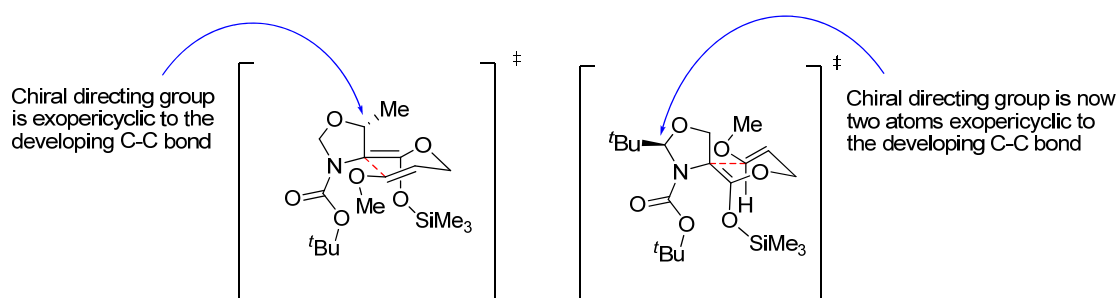
**Scheme 134 – Rearrangement of heteroproline allyl esters**

Of particular interest was the level of remote transfer of chirality seen in the rearrangements of the threonine derived substrates. The methyl group located on the oxazolidine acts to selectively direct the rearrangement from a single face.

This investigation has sought to combine an Ireland-Claisen rearrangement with the self-regeneration of stereocentres strategy pioneered by Seebach. The difficulties

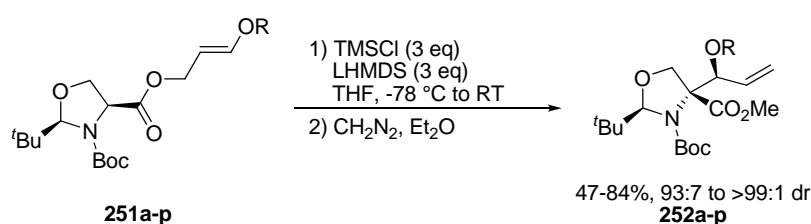


involved with such remote levels of stereocontrol can be inferred from the relatively scattered literature reports, with limited efficacy, of asymmetric rearrangements with chirality outside the cyclic transition state. In this novel rearrangement protocol, the chiral directing group is two atoms exopericyclic to the developing C-C bond (Figure 41).



**Figure 41 - Exopericyclic nature of the directing group in an Ireland-Claisen rearrangement**

Significantly, the rearrangement showed outstanding levels of diastereoselectivity, with complete transfer of chirality achieved. The generality of this reaction has shown to be impressive, with both enol ether substrates undergoing facile rearrangement (Scheme 135), and also those bearing carbon substitution on the allyl ester. A range of functional handles have been incorporated into the products, along with protecting groups, allowing access to dihydrofurans, benzofurans, *spiro*-lactones in addition to  $\beta,\beta'$ -dihydroxy- $\alpha$ -amino acid derivatives.



**Scheme 135 - Rearrangement scope: enol ether variation**

When shown in comparison to aldol reactions performed on a similar oxazolidine framework, the importance of this reaction can be clearly identified. Allowing considerable improvements in selectivity, along with a wide reaction scope, this rearrangement shows considerable potential for synthetic utility.

The ability to access chiral  $\beta,\beta'$ -dihydroxy- $\alpha$ -amino acid head groups with such high selectivity has allowed the total synthesis of the potent immunosuppressant mycestericin G (Figure 42). Both enantiomers of this natural product have been readily synthesised, which, along with XRD analysis of *o*-iodophenoxy rearrangement product **252i**, allowed for a revision in stereochemistry to that previously reported. Using the synthetic route developed in the synthesis of mycestericin G, the threonine analogue, (2*S*,3*R*)-2-amino-3-hydroxy-2-((*R*)-1-hydroxyethyl)-14-oxoicosanoic acid **296**, was also successfully synthesised. A key observation from these syntheses, was the effect steric interactions made on the success of the cross-metathesis.

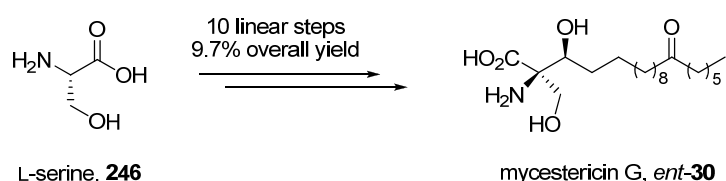


Figure 42 - Total synthesis of mycestericin G

Finally, a series of chiral diene ligands were synthesised based around the *tert*-butyloxazolidine core. From an extensive ligand screen, it was observed that substitution of the allyl olefin reduced either the reactivity, or the enantioselectivity of the conjugate addition, whilst the methyloxazolidine core suffered both from both poor reactivity and a decrease in enantioselectivity. With the allyl ligand **327c** chosen to explore the substrate scope, excellent enantioselectivities were obtained in the rhodium-catalysed conjugate addition reaction of 2-cyclohexenone with a variety of aryl boronic acids.

## 6.2 Future Work

There are several viable areas of research that this body of work could continue to explore. Whilst the SRS/Ireland-Claisen methodology has shown its synthetic applicability with the total synthesis of mycestericin G, there are several more natural products that remain a key target.

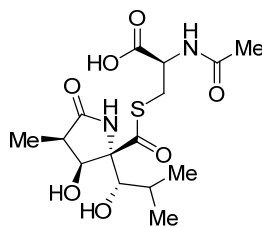


Figure 43 - Lactacystin

One particular target, lactacystin (Figure 43), would require further development in two key areas of the rearrangement. Firstly, the effects of internal olefin substitution would need to be probed. It can be seen from the retrosynthetic analysis that rearrangement of a 3-benzyloxy-2-methallyl ester would provide the core chirality required to complete the synthesis of 9-*epi*-lactacystin (Figure 44). However, no attempts have been made in this body of work to rearrange tri-substituted olefins of that nature. Secondly, to complete the synthesis of lactacystin itself, access to the alternative diastereomer is required. Since use of *Z*-enol ethers were unsuccessful in our attempts to obtain the alternative diastereomer, it would be desirable to develop a facile route, perhaps through use of a Mitsunobu reaction, to invert the stereochemistry.

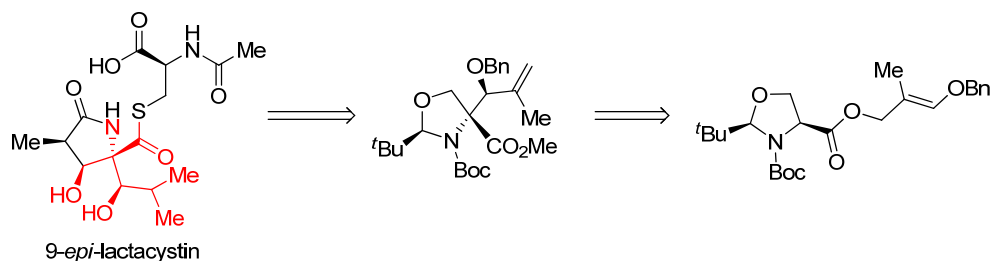
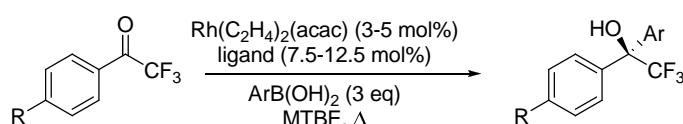


Figure 44 - Retrosynthesis of 9-*epi*-lactacystin

The logical continuation of the rhodium-catalysed conjugate addition is to continue to explore the scope of the reaction. Currently, with the sole exception of the 1-naphthaleneboronic acid, only *para*-substituted arylboronic acids have been investigated. To fully demonstrate the applicability of our catalyst/ligand system, a wide range of *ortho*-/*meta*-/*para*-substituted systems, containing both electron rich, and electron deficient systems need to be examined. Furthermore, it would be desirable to vary the  $\alpha,\beta$ -unsaturated ketone used as the acceptor in this reaction protocol. Not only would this incorporate variation in the cyclic ring size, but also attempt the conjugate addition on an acyclic substrate. There has been limited success to date in the conjugate

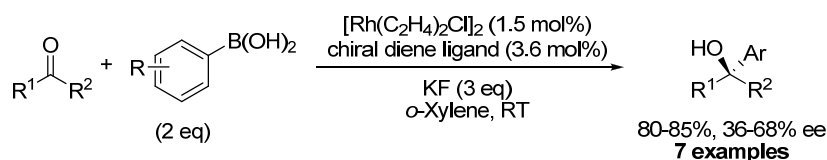
addition to an acyclic substrate utilising terminal diene ligands, so this would be a useful benchmark for the efficacy of our system.<sup>257</sup>

Rhodium-catalysed addition reactions of arylborons with aldehydes have recently been shown to be an attractive transformation.<sup>272-273</sup> The use of ketones has, however, largely been limited to activated ketones, such as the trifluoromethyl ketones used by Minnaard *et al.* (Scheme 136).



**Scheme 136 - Addition of arylboronic acids to trifluoromethyl ketones**

Unactivated ketones, meanwhile, have only been reported to be suitable substrates under special conditions. However, Hu *et al.* have recently reported a rhodium(I)/diene-catalysed addition reaction of arylborons with ketones.<sup>273</sup> With 23 examples they have shown this to be a general reaction, with moderate to good enantioselectivities obtained.



**Scheme 137 - Rh(I)/chiral diene-catalysed addition reactions of arylboronic acids with ketones**

These literature reports provide a vast scope with which to benchmark our *tert*-butyloxazolidine diene ligand **327c** against, and to hopefully push the boundaries of the current synthetic limitations.

## 7. EXPERIMENTAL

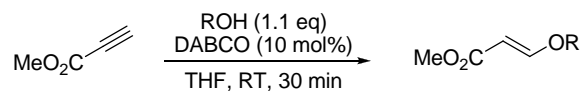
### 7.1 General Experimental Information

All reactions were carried out using anhydrous solvents and under an inert atmosphere of nitrogen. All reaction vessels were flame dried before use. Solvents were obtained by passing through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. All reagents were purchased from commercial suppliers: Acros Organics, Alfa Aesar, Sigma Aldrich or Novabiochem and used without further purification. Triethylamine was freshly distilled prior to use and chlorotrimethylsilane was freshly distilled from 10 % quinoline. All distilled materials were stored under nitrogen in a fridge. All reactions were monitored by thin layer chromatography (TLC) using pre-coated MN Alugram Sil G/UV254 silica gel 60 aluminium backed plates. Plates were developed using standard techniques, UV light followed by a chemical dip, usually  $\text{KMnO}_4$  and gentle heating. Flash chromatography was performed on chromatography grade, silica 60Å particle size 35-70 micron from Fisher Scientific using the solvent system as stated.

$^1\text{H}$  and  $^{13}\text{C}$  NMR was performed on Brüker Avance 250 ( $^1\text{H}$  250 MHz), Brüker Avance 300 ( $^1\text{H}$  300 MHz and  $^{13}\text{C}$  75 MHz), Brüker Avance 400 ( $^1\text{H}$  400 MHz and  $^{13}\text{C}$  100 MHz) and Brüker Avance 500 ( $^1\text{H}$  500 MHz and  $^{13}\text{C}$  125 MHz) as stated. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS) ( $\delta = 0.00$ ). Coupling constants are reported in Hertz (Hz) and signal multiplicity is denoted as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin.), sextet (sex.), septet (sept.), multiplet (m), and broad (br). Mass spectroscopy was performed on a Brüker  $\mu\text{TOF}$  using electrospray ionisation (ESI) in either positive or negative ionisation as stated. Infra-red spectroscopy was carried out using a Perkin Elmer Spectrum RX FT-IR system with KBr plates, using a thin film. Melting points were determined using a Bibby Scientific Melting point apparatus Stuart SMP10 digital. X-ray data was collected at 150 K on a Nonius KappaCCD area diffractometer using Mo-K $\alpha$  radiation ( $\lambda = 0.71073 \text{ \AA}$ ) and all structures were solved by direct methods and refined on all  $F^2$  data using SHELXL-97 suite of programs. Hydrogen atoms included in idealised positions and refined using the riding model.

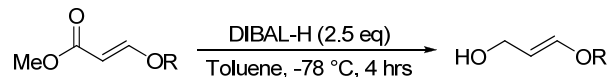
## 7.2 General Experimental Procedures

### General Procedure I for the preparation of Vinylogous Carbonates<sup>172</sup>



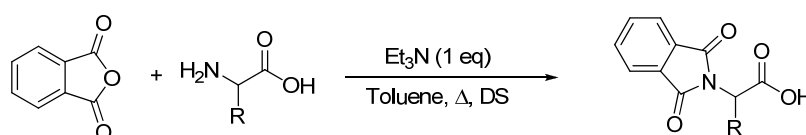
To a stirred solution of 1,4-diazabicyclo[2.2.2]octane (10 mol%) and alcohol (1.1 eq) in THF (150 ml) at room temperature was added methyl propiolate (1.0 eq) *via* syringe pump over 10 minutes, before stirring at room temperature for a further 30 minutes. Sodium hydroxide (10% solution, 200 ml) was added and the aqueous was extracted with DCM (4 × 100 ml), combined, washed with brine (3 × 150 ml), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. Product ester was isolated after subsequent purification by flash chromatography.

### General Procedure II for the preparation of Synthesis of Enol Ethers<sup>172</sup>



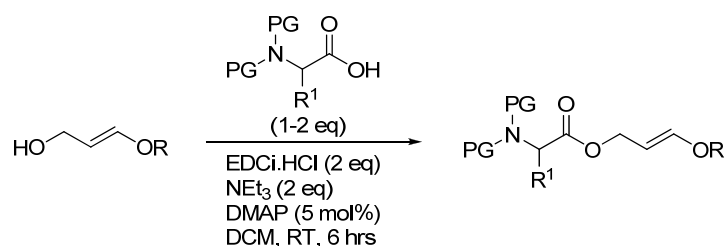
To a stirred solution of *trans*-methyl 3-alkoxyacrylate (1.0 eq) in toluene (10 mL) at -78 °C was added DIBAL-H (1M in tol., 2.5 eq) at a rate of 1 mL min<sup>-1</sup>. After addition the reaction was stirred at -78 °C for 4-8 hrs before being poured into an ice-cold solution of saturated Rochelle salt (150 mL) and EtOAc (150 mL). The biphasic mixture was stirred vigorously at room temperature for 2 hours before extracting with EtOAc (3 × 75 mL). The organics were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo* to afford the enol ether without the need for further purification.

### General Procedure III for the preparation of *N*-Phthaloyl Amino Acids



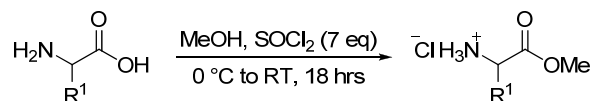
To a stirred solution of amino acid (1.0 eq) and phthalic anhydride (1.01 eq) in toluene was added triethylamine (1.0 eq) and refluxed under Dean-Stark conditions until the heterogeneous mixture went into solution and sufficient water had been evolved (~ 24 hrs). The solution was allowed to cool to room temperature and washed with 10% citric acid (aq) ( $3 \times 75$  mL), back extracted with EtOAc ( $1 \times 100$  mL), dried and concentrated *in vacuo* to afford the *N*-phthaloyl amino acid without the need for further purification.

#### General Procedure IV for Carbodiimide Promoted Coupling Reactions

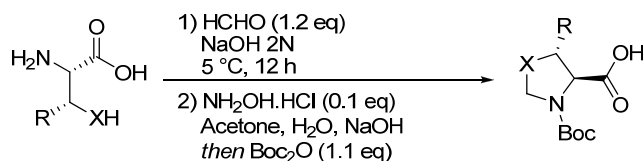


To a stirred solution of *N*-protected amino acid (2.0 eq) in DCM was added EDCi.HCl (2.0 eq), triethylamine (2.0 eq), catalytic DMAP (5 mol%) and the enol ether (1.0 eq). The reaction is stirred at room temperature until consumption of enol ether was observed by TLC. The reaction mixture was diluted with DCM (30 mL) before washing with  $\text{NaHCO}_3$  (sat) ( $3 \times 50$  mL), 10% citric acid ( $3 \times 50$  mL), brine ( $1 \times 50$  mL) and dried over  $\text{Na}_2\text{SO}_4$ . Concentration *in vacuo* afforded the enol amino esters without the need for further purification.

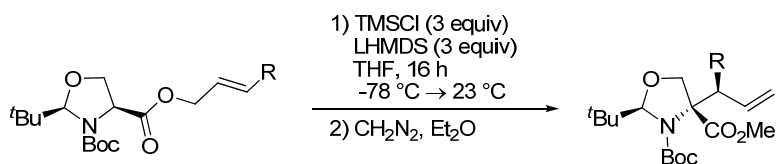
#### General Procedure V for the preparation of Amino Acid Methyl Esters Hydrochloride



To a solution of amino acid (1.0 eq) in MeOH (350 mL) at 0 °C was added thionyl chloride (2.0-7.0 eq) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 18 hours. Solvent was removed *in vacuo* and crude solid was re-dissolved in acetone (50 mL) and concentrated *in vacuo* to afford amino acid methyl esters without the need for further purification.

**General Procedure VI for the preparation of *N*-Boc Heteroprolines<sup>184</sup>**

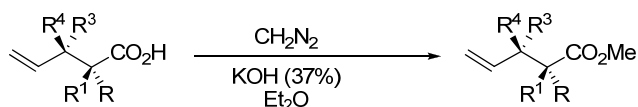
A solution of amino acid (1.0 eq) and formaldehyde (37% aq, 1.2 eq) in 2N NaOH (15 mL) was allowed to stand in the fridge overnight. Then NH<sub>2</sub>OH.HCl (0.1 eq), NaOH (0.1 eq) in H<sub>2</sub>O (2.5 mL) and acetone (17.5 mL) was added at 0 °C. Boc<sub>2</sub>O (1.1 eq) was added at room temperature and the reaction mixture stirred for a further 3 hours. The reaction mixture was diluted with water (50 mL) and washed with Et<sub>2</sub>O (1 × 50 mL). The aqueous phase was acidified to pH 3 with 20% citric acid and extracted with EtOAc (3 × 50 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to afford *N*-Boc heteroproline.

**General Procedure VII for the Ireland-Claisen Rearrangement of Oxazolidine Allyl Esters**

To a stirred solution of oxazolidine allyl ester (1.0 eq) in THF at -78 °C was added TMSCl (3.0 eq). After 10 mins LHMDS (1M, 3.0 eq) was added *via* syringe pump at an addition rate of 10 mL hr<sup>-1</sup> and the reaction mixture allowed to warm to room temperature after a period of 30 mins, and stirred for 18 hours. The reaction was quenched by the addition of 1N HCl and brine solution (1:1) and extracted with DCM (3 × 15 mL) and EtOAc (1 × 15 mL). The organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to afford the crude acid. Treatment with diazomethane (according to general procedure VIII) affords the crude amino ester.

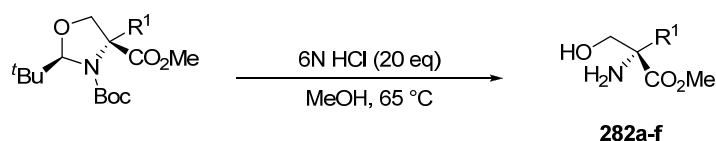


### General Procedure VIII for the Diazomethane Methylation of Carboxylic Acids



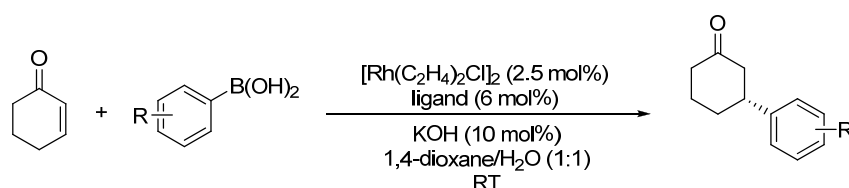
To a solution of the crude acid (1.0 eq) in diethyl ether at 0 °C was added an ethereal solution of diazomethane generated from *N*-nitrosomethyl urea (2.0 eq) and KOH (37%) using sigma aldrich's mini diazald kit. Once esterification was complete (yellow colour persists), the mix was quenched with glacial acetic acid then basified with NaHCO<sub>3</sub> (sat). The organics were extracted with EtOAc (5 × 15 ml), dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*.

### General Procedure IX for the Deprotection and Acid Hydrolysis of *N*-Boc Oxazolidines



To a solution of *N*-Boc oxazolidine (1.0 eq) in MeOH was added 6N HCl (20 eq) and the reaction mixture refluxed until consumption of starting material was observed by TLC. The reaction mixture was allowed to cool to room temperature and concentrated *in vacuo* to afford the crude hydrochloride salt. This was treated with saturated sodium bicarbonate (20 mL) and extracted with DCM (3 × 10 mL), dried over anhydrous magnesium sulphate and concentrated *in vacuo* to afford the crude amino esters.

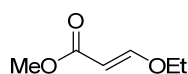
### General Procedure X for Rhodium-Catalysed Conjugate Additions



A solution of boronic acid (1.5 eq), bis(ethylene)rhodium(I) chloride dimer (2.5 mol%) and ligand (6 mol%) in 1,4-dioxane (0.9 mL) was allowed to stir at room temperature for 15 minutes. 2-Cyclohexenone and potassium hydroxide (aq) (0.075M, 10 mol%) were added and the reaction mixture immediately concentrated *in vacuo* and purified by flash chromatography to afford the pure arylcyclohexanones.

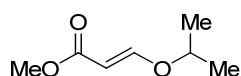
### 7.3 Compound Characterisation

#### (*E*)-Methyl 3-ethoxyacrylate (217b)



DABCO (270 mg, 2.38 mmol) in THF (200 mL), ethanol (1.21 g, 26.2 mmol) and methyl propiolate (2.12 mL, 23.8 mmol) were combined according to general procedure I (reaction time: 45 minutes). Purified by flash chromatography (10:1 Pet/EtOAc) to afford the pure vinylogous carbonate as a colourless oil (2.72 g, 88%). <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 1.31 (3H, t, *J* = 7.0 Hz), 3.66 (3H, s), 3.88 (2H, q, *J* = 7.0 Hz), 5.17 (1H, d, *J* = 12.6 Hz), 7.56 (1H, d, *J* = 12.6 Hz); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>) δ<sub>C</sub> 14.4, 51.0, 66.7, 96.0, 162.4, 168.3. All analytical data is in accordance with reported literature values.<sup>172</sup>

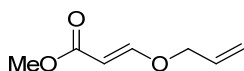
#### (*E*)-Methyl 3-isopropoxyacrylate (217c)



DABCO (270 mg, 2.38 mmol) in THF (200 mL), propan-2-ol (1.57 g, 26.2 mmol) and methyl propiolate (2.12 mL, 23.8 mmol) were combined according to general procedure I (reaction time: 30 minutes). Purified by flash chromatography (10:1 Pet/EtOAc) followed by distillation under vacuum to afford the pure vinylogous carbonate as a colourless oil (2.27 g, 73%). <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 1.24 (6H, d, *J* = 6.2 Hz), 3.63 (3H, s), 4.18 (1H, sept, *J* = 6.2 Hz), 5.18 (1H, d, *J* = 12.5 Hz), 7.47 (1H, d, *J* = 12.5

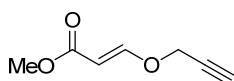
Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  21.9, 50.8, 75.5, 96.8, 161.6, 168.4. All analytical data is in accordance with reported literature values.<sup>173</sup>

**(E)-Methyl 3-(allyloxy)acrylate (217d)**

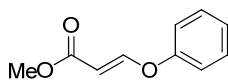


DABCO (270 mg, 2.38 mmol) in THF (100 mL), allyl alcohol (1.37 g, 23.6 mmol) and methyl propiolate (2.12 mL, 23.8 mmol) were combined according to general procedure I (reaction time: 40 minutes). Purified by flash chromatography (10:1 Pet/EtOAc) to afford the pure vinylogous carbonate as a colourless oil (2.85 g, 85%).  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  3.60 (3H, s), 4.30 (2H, dt,  $J = 5.3, 1.5$  Hz), 5.16 (1H, d,  $J = 12.6$  Hz), 5.22 (1H, dq,  $J = 10.3, 1.5$  Hz), 5.28 (1H, dq,  $J = 17.2, 1.5$  Hz), 5.85 (1H, ddt,  $J = 17.2, 10.3, 5.3$  Hz), 7.49 (1H, d,  $J = 12.6$  Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  50.9, 71.5, 96.8, 118.7, 131.7, 161.9, 167.9. All analytical data is in accordance with reported literature values.<sup>172</sup>

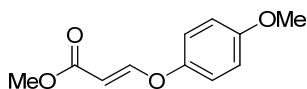
**(E)-Methyl 3-(prop-2-ynoxy)acrylate (217e)**



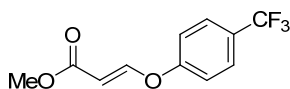
DABCO (204 mg, 1.82 mmol) in THF (250 mL), propargyl alcohol (1.16 mL, 20.0 mmol) and methyl propiolate (1.62 mL, 18.2 mmol) were combined according to general procedure I (reaction time: 45 minutes). Purified by flash chromatography (10:1 Pet/EtOAc) to afford the pure vinylogous carbonate as a colourless oil (2.19 g, 86%).  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  2.60 (1H, t,  $J = 2.6$  Hz), 3.71 (3H, s), 4.53 (2H, d,  $J = 2.6$  Hz), 5.35 (1H, d,  $J = 12.7$  Hz), 7.58 (1H, d,  $J = 12.7$  Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  51.2, 58.1, 76.6, 77.0, 98.3, 160.6, 167.6. All analytical data is in accordance with reported literature values.<sup>173</sup>

**(E)-Methyl 3-phenoxyacrylate (217f)**

DABCO (270 mg, 2.38 mmol) in THF (200 mL), phenol (2.46 g, 26.2 mmol) and methyl propiolate (2.12 mL, 23.8 mmol) were combined according to general procedure I (reaction time: 45 minutes). Purified by flash chromatography (10:1 Pet/EtOAc) to afford the pure vinylogous carbonate as a colourless oil (4.34 g, 98%).  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  3.74 (3H, s), 5.58 (1H, d,  $J = 12.4$  Hz), 7.08 (2H, d,  $J = 8.4$  Hz), 7.21 (1H, t,  $J = 7.5$  Hz), 7.39 (2H, t,  $J = 7.5$  Hz), 7.83 (1H, d,  $J = 12.4$  Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  51.3, 101.8, 118.0, 125.0, 130.0, 155.9, 159.2, 167.6. All analytical data is in accordance with reported literature values.<sup>172</sup>

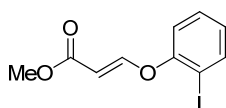
**(E)-Methyl 3-(4-methoxyphenoxy)acrylate (217g)**

DABCO (270 mg, 2.38 mmol) in THF (200 mL), 4-methoxyphenol (3.25 g, 26.2 mmol) and methyl propiolate (2.12 mL, 23.8 mmol) were combined according to general procedure I (reaction time: 45 minutes). Purified by flash chromatography (6:1 Pet/EtOAc) to afford the pure vinylogous carbonate as a colourless oil (4.49 g, 91%).  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  3.73 (3H, s), 3.81 (3H, s), 5.48 (1H, d,  $J = 12.6$  Hz), 6.89 (2H, m), 7.00 (2H, m), 7.76 (1H, d,  $J = 12.6$  Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  51.7, 56.1, 101.3, 115.3, 119.8, 149.9, 157.3, 160.8, 168.2. All analytical data is in accordance with reported literature values.<sup>172</sup>

**(E)-Methyl 3-(4-(trifluoromethyl)phenoxy)acrylate (217h)**

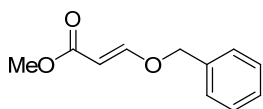
DABCO (135 mg, 1.19 mmol) in THF (200 mL), 4-(trifluoromethyl)phenol (2.12 g, 13.1 mmol) and methyl propiolate (1.06 mL, 11.9 mmol) were combined according to general procedure I (reaction time: 45 minutes). Purified by flash chromatography (15:1 Pet/EtOAc) to afford the pure vinylogous carbonate as a colourless oil (2.72 g, 93%). Mpt: 60-61 °C;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  3.74 (3H, s), 5.66 (1H, d,  $J = 12.2$  Hz), 7.16 (2H, m), 7.64 (2H, m), 7.80 (1H, d,  $J = 12.2$  Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  51.4, 103.6, 117.8, 122.7, 124.9, 127.4 (q,  $J = 3.6$  Hz), 157.2, 158.1, 167.1. All analytical data is in accordance with reported literature values.<sup>172</sup>

**(*E*)-Methyl 3-(2-iodophenoxy)acrylate (217i)**



DABCO (116 mg, 1.03 mmol) in THF (200 mL), 2-iodophenol (2.50 g, 11.4 mmol) and methyl propiolate (916  $\mu\text{L}$ , 10.3 mmol) were combined according to general procedure I (reaction time: 45 minutes). Purified by flash chromatography (6:1 Pet/EtOAc) to afford the pure vinylogous carbonate as a colourless oil (2.91 g, 93%).  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  3.74 (3H, s), 5.52 (1H, d,  $J = 12.4$  Hz), 6.96 (1H, t,  $J = 7.5$  Hz), 7.07 (1H, d,  $J = 7.5$  Hz), 7.38 (1H, t,  $J = 7.8$  Hz), 7.72 (1H, d,  $J = 12.4$  Hz), 7.85 (1H, d,  $J = 7.8$  Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  51.4, 87.8, 102.3, 119.1, 127.0, 130.0, 140.0, 155.1, 159.0, 167.3. All analytical data is in accordance with reported literature values.<sup>172</sup>

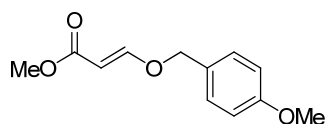
**(*E*)-Methyl 3-(benzyloxy)acrylate (217j)**



DABCO (110 mg, 0.970 mmol) in THF (40 mL), benzyl alcohol (1.08 g, 9.99 mmol) and methyl propiolate (890  $\mu\text{L}$ , 9.99 mmol) were combined according to general procedure I (reaction time: 40 minutes). Purified by flash chromatography (10:1 Pet/EtOAc) followed by distillation under vacuum to afford the pure vinylogous carbonate as a colourless oil (1.65 g, 86%).  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  3.71 (3H,

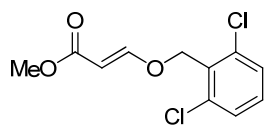
s), 4.91 (2H, s), 5.34 (1H, d,  $J = 12.7$  Hz), 7.34–7.42 (5H, m), 7.69 (1H, d,  $J = 12.7$  Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  51.1, 72.9, 97.2, 127.7, 128.5, 128.7, 135.2, 162.1, 168.0. All analytical data is in accordance with reported literature values.<sup>172</sup>

**(*E*)-Methyl 3-(4-methoxybenzyloxy)acrylate (217k)**

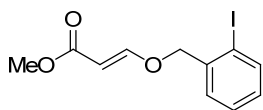


DABCO (270 mg, 2.38 mmol) in THF (200 mL), 4-methoxybenzyl alcohol (3.25 mL, 26.2 mmol) and methyl propiolate (2.12 mL, 23.8 mmol) were combined according to general procedure I (reaction time: 30 minutes). Purified by flash chromatography (10:1 Pet/EtOAc) to afford the pure vinylogous carbonate as a colourless oil (4.92 g, 93%).  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  3.71 (3H, s), 3.83 (3H, s), 4.84 (2H, s), 5.32 (1H, d,  $J = 12.5$  Hz), 6.92 (2H, m), 7.28 (2H, m), 7.67 (1H, d,  $J = 12.5$  Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  51.1, 55.3, 72.8, 97.0, 114.1, 127.2, 129.6, 159.9, 162.2, 168.1. All analytical data is in accordance with reported literature values.<sup>172</sup>

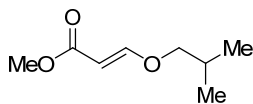
**(*E*)-Methyl 3-(2,6-dichlorobenzyloxy)acrylate (217l)**



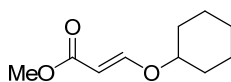
DABCO (270 mg, 2.38 mmol) in THF (300 mL), 2,6-dichlorobenzyl alcohol (4.63 g, 26.2 mmol) and methyl propiolate (2.12 mL, 23.8 mmol) were combined according to general procedure I (reaction time: 30 minutes). Purified by flash chromatography (10:1 Pet/EtOAc) to afford the pure vinylogous carbonate as a colourless oil (3.82 g, 62%).  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  3.73 (3H, s), 5.16 (2H, s), 5.39 (1H, d,  $J = 12.6$  Hz), 7.25–7.28 (1H, m), 7.35 (1H, s), 7.37 (1H, s), 7.71 (1H, d,  $J = 12.6$  Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  51.2, 67.5, 97.1, 128.5, 130.7, 131.0, 137.0, 162.1, 167.9. All analytical data is in accordance with reported literature values.<sup>173</sup>

**(E)-Methyl 3-(2-iodobenzyloxy)acrylate (217m)**

DABCO (270 mg, 2.38 mmol) in THF (200 mL), 2-iodobenzyl alcohol (6.12 g, 26.2 mmol) and methyl propiolate (2.12 mL, 23.8 mmol) were combined according to general procedure I (reaction time: 45 minutes). Purified by flash chromatography (6:1 Pet/EtOAc) to afford the pure vinylogous carbonate as a colourless oil (6.85 g, 91%).  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  3.73 (3H, s), 4.91 (2H, s), 5.37 (1H, d,  $J = 12.5$  Hz), 7.04–7.07 (1H, m), 7.36–7.40 (2H, m), 7.71 (1H, d,  $J = 12.5$  Hz), 7.87 (1H, d,  $J = 8.1$  Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  51.2, 76.4, 97.4, 97.5, 128.5, 128.8, 130.1, 137.5, 139.5, 161.7, 167.9. All analytical data is in accordance with reported literature values.<sup>172</sup>

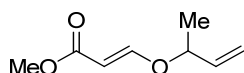
**(E)-Methyl 3-isobutoxyacrylate (217n)**

DABCO (270 mg, 2.38 mmol) in THF (200 mL), 2-methyl-1-propanol (2.42 g, 26.2 mmol) and methyl propiolate (2.12 mL, 23.8 mmol) were combined according to general procedure I (reaction time: 45 minutes). Purified by flash chromatography (6:1 Pet/EtOAc) to afford the pure vinylogous carbonate as a colourless oil (3.24 g, 86%).  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  0.91 (6H, d,  $J = 6.7$  Hz), 1.95 (1H, oct,  $J = 6.7$  Hz), 3.56 (2H, d,  $J = 6.7$  Hz), 3.64 (3H, s), 5.14 (1H, d,  $J = 12.7$  Hz), 7.55 (1H, d,  $J = 12.7$  Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  18.8, 28.0, 50.9, 77.4, 95.8, 162.8, 168.2. All analytical data is in accordance with reported literature values.<sup>172</sup>

**(E)-Methyl 3-(cyclohexyloxy)acrylate (217o)**

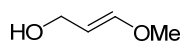
DABCO (270 mg, 2.38 mmol) in THF (400 mL), cyclohexanol (2.62 g, 26.2 mmol) and methyl propiolate (2.12 mL, 23.8 mmol) were combined according to general procedure I (reaction time: 1 hour). Purified by flash chromatography (15:1 Pet/EtOAc) to afford the pure vinylogous carbonate as a colourless oil (1.58 g, 36%). FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2937, 2861, 1707, 1638, 1619; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  1.23–1.56 (6H, m), 1.71–1.76 (2H, m), 1.89–1.93 (2H, m), 3.69 (3H, s), 3.93 (1H, sept,  $J$  = 4.1 Hz), 5.25 (1H, d,  $J$  = 12.7 Hz), 7.56 (1H, d,  $J$  = 12.7 Hz); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  23.4, 25.2, 31.8, 51.0, 81.0, 96.8, 161.8, 168.6; HRMS (ESI, +ve)  $m/z$  calcd. for C<sub>10</sub>H<sub>16</sub>O<sub>3</sub>Na 207.0997, found: 207.0994 (M+Na)<sup>+</sup>.

**(*E*)-Methyl 3-(but-3-en-2-yloxy)acrylate (217p)**



DABCO (204 mg, 1.82 mmol) in THF (200 mL), 3-buten-2-ol (1.44 g, 20.0 mmol) and methyl propiolate (1.62 mL, 18.2 mmol) were combined according to general procedure I (reaction time: 30 minutes). Purified by flash chromatography (10:1 Pet/EtOAc) to afford the pure vinylogous carbonate as a colourless oil (2.30 g, 81%). FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2986, 2952, 1708, 1639, 1621; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  1.26 (3H, d,  $J$  = 6.4 Hz), 3.56 (3H, s), 4.39 (1H, app. quin,  $J$  = 6.4 Hz), 5.09–5.18 (3H, m), 5.70 (1H, ddd,  $J$  = 17.1, 10.5, 6.4 Hz), 7.40 (1H, d,  $J$  = 12.5 Hz); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  20.5, 50.7, 79.4, 97.5, 116.9, 137.5, 161.2, 168.0; HRMS (ESI, +ve)  $m/z$  calcd. for C<sub>8</sub>H<sub>12</sub>O<sub>3</sub>Na 179.0684, found: 179.0676 (M+Na)<sup>+</sup>.

**(*E*)-3-(Methoxy)prop-2-enol (218a)**

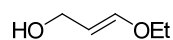


Methyl *trans*-3-methoxyacrylate (1.85 mL, 17.2 mmol) was reduced according to general procedure II (reaction time: 4 hours) to afford the product as a yellow oil (1.17 g, 77%). <sup>1</sup>H NMR (500 MHz, d<sub>6</sub>-acetone)  $\delta_{\text{H}}$  3.35 (1H, t,  $J$  = 5.7 Hz), 3.51 (3H, s), 3.96 (2H, app. t,  $J$  = 7.0 Hz), 4.96 (1H, dt,  $J$  = 12.7, 7.0 Hz), 6.51 (1H, d,  $J$  = 12.7 Hz);



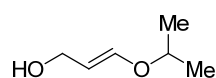
$^{13}\text{C}$  NMR (125 MHz,  $\text{d}_6$ -acetone)  $\delta_{\text{C}}$  55.1, 59.1, 102.9, 149.5. All analytical data is in accordance with literature precedence.<sup>172</sup>

**(*E*)-3-Ethoxyprop-2-en-1-ol (218b)**



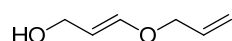
(*E*)-methyl 3-ethoxyacrylate (1.59 g, 12.2 mmol) was reduced according to general procedure II (reaction time: 6 hours) to afford the product as a colourless oil (1.10 g, 88%).  $^1\text{H}$  NMR (500MHz, DMSO)  $\delta_{\text{H}}$  1.19 (3H, t,  $J = 7.1$  Hz), 3.70 (2H, q,  $J = 7.1$  Hz), 3.83 (2H, ddd,  $J = 5.6, 4.7, 1.3$  Hz), 4.40 (1H, t,  $J = 5.6$  Hz), 4.86 (1H, dt,  $J = 12.9, 6.9$  Hz), 6.42 (1H, d,  $J = 12.9$  Hz);  $^{13}\text{C}$  NMR (125MHz, DMSO)  $\delta_{\text{C}}$  15.1, 59.0, 64.6, 104.4, 148.5. All analytical data is in accordance with literature precedence.<sup>172</sup>

**(*E*)-3-Isopropoxyprop-2-en-1-ol (218c)**



(*E*)-Methyl 3-isopropoxyacrylate (2.08 g, 14.4 mmol) was reduced according to general procedure II (reaction time: 4 hours) to afford the product as a colourless oil (1.41 g, 76%).  $^1\text{H}$  NMR (500MHz,  $\text{d}_6$ -acetone)  $\delta_{\text{H}}$  1.15 (6H, d,  $J = 6.2$  Hz), 3.81 (2H, app. t,  $J = 6.5$  Hz), 4.00 (1H, quin,  $J = 6.2$  Hz), 4.36 (1H, t,  $J = 5.4$  Hz), 4.88 (1H, dt,  $J = 12.5, 6.5$  Hz), 6.33 (1H, d,  $J = 12.5$  Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{d}_6$ -acetone)  $\delta_{\text{C}}$  22.4, 59.0, 72.3, 105.7, 147.6. All analytical data is in accordance with literature precedence.<sup>173</sup>

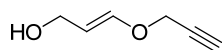
**(*E*)-3-(Allyloxy)prop-2-en-1-ol (218d)**



(*E*)-Methyl 3-(allyloxy)acrylate (1.38 g, 12.1 mmol) was reduced according to general procedure II (reaction time: 6 hours) to afford the product as a yellow oil (0.78 g, 71%).  $^1\text{H}$  NMR (500 MHz,  $\text{d}_6$ -DMSO)  $\delta_{\text{H}}$  3.83 (2H, ddd,  $J = 7.0, 5.5, 1.2$  Hz), 4.21 (2H, dt,  $J = 5.3, 1.7$  Hz), 4.43 (1H, t,  $J = 5.5$  Hz), 4.92 (1H, dt,  $J = 13.8, 7.0$  Hz), 5.20 (1H, dq,  $J =$

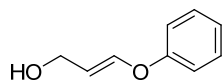
10.4, 1.7 Hz), 5.31 (1H, dq,  $J = 17.3, 1.7$  Hz), 5.94 (1H, ddt,  $J = 17.3, 10.4, 5.3$  Hz), 6.44 (1H, d,  $J = 13.8$  Hz);  $^{13}\text{C}$  NMR (125 MHz,  $\text{d}_6\text{-DMSO}$ )  $\delta_{\text{C}}$  58.5, 69.9, 105.1, 117.6, 134.3, 148.2. All analytical data is in accordance with literature precedence.<sup>172</sup>

**(*E*)-3-(Prop-2-ynyloxy)prop-2-en-1-ol (218e)**



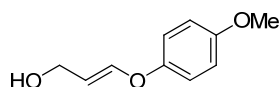
(*E*)-methyl 3-(prop-2-ynyloxy)acrylate (2.07 g, 14.8 mmol) was reduced according to general procedure II (reaction time: 6 hours) to afford the product as a colourless oil (1.37 g, 83%).  $^1\text{H}$  NMR (500MHz,  $\text{d}_6\text{-acetone}$ )  $\delta_{\text{H}}$  2.60 (1H, dt,  $J = 2.4, 0.8$  Hz), 4.06 (2H, d,  $J = 7.2$  Hz), 4.43 (2H, d,  $J = 2.4$  Hz), 5.17 (1H, dt,  $J = 12.7, 7.2$  Hz), 6.52 (1H, d,  $J = 12.7$  Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{d}_6\text{-acetone}$ )  $\delta_{\text{C}}$  57.0, 60.1, 75.3, 78.5, 105.4, 148.1. All analytical data is in accordance with literature precedence.<sup>173</sup>

**(*E*)-3-Phenoxyprop-2-en-1-ol (218f)**



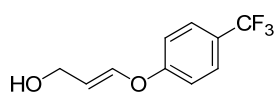
(*E*)-Methyl 3-(phenoxy)acrylate (1.02 g, 6.79 mmol) was reduced according to general procedure II (reaction time: 6 hours) to afford the product as a colourless oil (0.60 g, 53%).  $^1\text{H}$  NMR (500 MHz,  $\text{d}_6\text{-acetone}$ )  $\delta_{\text{H}}$  3.70 (1H, t,  $J = 5.4$  Hz), 4.11 (2H, app. t,  $J = 6.6$  Hz), 5.49 (1H, dt,  $J = 12.3, 6.6$  Hz), 6.81 (1H, d,  $J = 12.3$  Hz), 7.04 (2H, d,  $J = 8.4$  Hz), 7.08 (1H, t,  $J = 7.5$  Hz), 7.36 (2H, d,  $J = 7.5$  Hz);  $^{13}\text{C}$  NMR (125 MHz,  $\text{d}_6\text{-acetone}$ )  $\delta$ : 58.4, 112.5, 116.4, 122.8, 129.7, 143.8, 157.2. All analytical data is in accordance with literature precedence.<sup>172</sup>

**(*E*)-3-(4-Methoxyphenoxy)prop-2-en-1-ol (218g)**



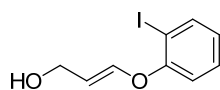
(*E*)-Methyl 3-(4-methoxyphenoxy)acrylate (1.15 g, 5.52 mmol) was reduced according to general procedure II (reaction time: 6 hours) to afford the product as a colourless oil (0.64 g, 64%).  $^1\text{H}$  NMR (500MHz,  $\text{d}_6$ -acetone)  $\delta_{\text{H}}$  4.10 (1H, t,  $J = 5.6$  Hz), 4.28 (3H, s), 4.58 (2H, app. t,  $J = 5.6$  Hz), 5.88 (1H, dt,  $J = 12.2, 6.7$  Hz), 7.22 (1H, d,  $J = 12.2$  Hz), 7.42 (2H, m, ArH), 7.48 (2H, m, ArH);  $^{13}\text{C}$  NMR (125MHz,  $\text{d}_6$ -acetone)  $\delta_{\text{C}}$  55.0, 58.5, 111.0, 114.7, 117.9, 145.3, 150.9, 155.7. All analytical data is in accordance with literature precedence.<sup>172</sup>

**(*E*)-3-(4-(Trifluoromethyl)phenoxy)prop-2-en-1-ol (218h)**

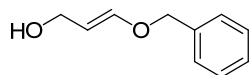


(*E*)-Methyl 3-(4-(trifluoromethyl)phenoxy)acrylate (2.55 g, 10.4 mmol) was reduced according to general procedure II (reaction time: 6 hours) to afford the product as a colourless oil (2.14 g, 95%).  $^1\text{H}$  NMR (500MHz,  $\text{d}_6$ -acetone)  $\delta_{\text{H}}$  3.76 (1H, br s), 3.96 (2H, dd,  $J = 6.5, 1.3$  Hz), 5.43 (1H, dt,  $J = 12.0, 6.5$  Hz), 6.66 (1H, dt,  $J = 12.0, 1.3$  Hz), 6.98 (2H, m), 7.44 (2H, m);  $^{13}\text{C}$  NMR (125MHz,  $\text{d}_6$ -acetone)  $\delta_{\text{C}}$  59.6, 116.0, 117.7, 125.3, 127.6, 128.4 (q,  $J = 4.0$  Hz), 143.8, 161.1. All analytical data is in accordance with literature precedence.<sup>172</sup>

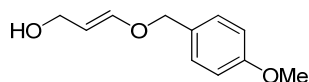
**(*E*)-3-(2-Iodophenoxy)prop-2-en-1-ol (218i)**



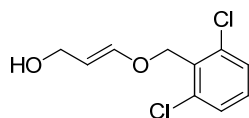
(*E*)-Methyl 3-(2-iodophenoxy)acrylate (1.34 g, 4.41 mmol) was reduced according to general procedure II (reaction time: 6 hours) to afford the product as a colourless oil (1.00 g, 82%).  $^1\text{H}$  NMR (500MHz,  $\text{d}_6$ -acetone)  $\delta_{\text{H}}$  3.59 (1H, t,  $J = 5.7$  Hz), 3.99 (2H, dt,  $J = 5.7, 1.4$  Hz), 5.40 (1H, dt,  $J = 12.1, 6.6$  Hz), 6.63 (1H, dt,  $J = 12.1, 1.4$  Hz), 6.97 (1H, dd,  $J = 7.5, 1.4$  Hz), 7.25–7.31 (1H, m), 7.72 (1H, dd,  $J = 7.9, 1.4$  Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{d}_6$ -acetone)  $\delta_{\text{C}}$  59.6, 87.4, 115.0, 117.7, 126.2, 131.2, 141.0, 144.9, 157.6. All analytical data is in accordance with literature precedence.<sup>172</sup>

**(*E*)-3-(Benzyloxy)prop-2-enol (218j)**

(*E*)-Methyl 3-(benzyloxy)acrylate (2.15 g, 11.2 mmol) was reduced according to general procedure II (reaction time: 4 hours) to afford the product as a colourless oil (1.56 g, 80%).  $^1\text{H}$  NMR (500 MHz,  $\text{d}_6$ -DMSO)  $\delta_{\text{H}}$  3.86 (2H, t,  $J = 6.3$  Hz), 4.47 (1H, t,  $J = 5.3$  Hz), 4.75 (2H, s), 5.02 (1H, m), 6.55 (1H, d,  $J = 13.1$  Hz), 7.32–7.39 (5H, m);  $^{13}\text{C}$  NMR (125 MHz,  $\text{d}_6$ -DMSO)  $\delta_{\text{C}}$  58.9, 71.0, 105.4, 126.9, 128.2, 128.8, 137.7, 148.4. All analytical data is in accordance with literature precedence.<sup>172</sup>

**(*E*)-3-(4-Methoxybenzyloxy)prop-2-en-1-ol (218k)**

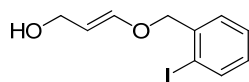
(*E*)-Methyl 3-(4-methoxybenzyloxy)acrylate (4.88 g, 21.9 mmol) was reduced according to general procedure II (reaction time: 7 hours) to afford the product as a colourless oil (3.82 g, 90%).  $^1\text{H}$  NMR (500MHz, DMSO)  $\delta_{\text{H}}$  3.75 (3H, s), 3.84 (2H, t,  $J = 5.6$  Hz), 4.45 (1H, t,  $J = 5.6$  Hz), 4.66 (2H, s), 4.98 (1H, dt,  $J = 12.8, 7.1$  Hz), 6.52 (1H, d,  $J = 12.8$  Hz), 6.93 (2H, m), 7.29 (2H, m);  $^{13}\text{C}$  NMR (125MHz, DMSO)  $\delta_{\text{C}}$  55.5, 58.9, 70.8, 105.2, 113.9, 128.4, 129.6, 148.4, 159.4. All analytical data is in accordance with literature precedence.<sup>172</sup>

**(*E*)-Methyl 3-(2,6-dichlorobenzyloxy)acrylate (218l)**

(*E*)-Methyl 3-(2,6-dichlorobenzyloxy)acrylate (2.36 g, 9.03 mmol) was reduced according to general procedure II (reaction time: 4 hours) to afford the product as a colourless oil (1.93 g, 91%). Mpt: 80–83 °C;  $^1\text{H}$  NMR (500MHz,  $\text{d}_6$ -acetone)  $\delta_{\text{H}}$  3.46 (1H, t,  $J = 5.9$  Hz), 4.02 (2H, app. t,  $J = 6.8$  Hz), 5.03 (2H, s), 5.34 (1H, dt,  $J = 12.4, 6.8$

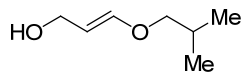
Hz), 6.63 (1H, d,  $J = 12.4$  Hz), 7.41–7.51 (3H, m);  $^{13}\text{C}$  NMR (125MHz,  $\text{d}_6$ -acetone)  $\delta_{\text{C}}$  59.2, 65.5, 104.8, 128.6, 131.0, 132.4, 136.5, 148.2. All analytical data is in accordance with literature precedence.<sup>173</sup>

**(*E*)-3-(2-Iodobenzyloxy)prop-2-en-1-ol (218m)**



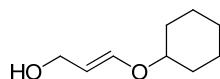
(*E*)-Methyl 3-(2-Iodobenzyloxy)acrylate 1.08 g, 3.72 mmol) was reduced according to general procedure II (reaction time: 6 hours) to afford the product as a colourless oil (0.88 g, 89%).  $^1\text{H}$  NMR (500MHz,  $\text{d}_6$ -acetone)  $\delta_{\text{H}}$  3.44 (1H, t,  $J = 5.3$  Hz), 4.01 (2H, t,  $J = 7.0$  Hz), 4.78 (2H, s), 5.14 (1H, dt,  $J = 12.3, 7.0$  Hz), 6.63 (1H, d,  $J = 12.3$  Hz), 7.11 (1H, td,  $J = 7.6, 1.7$  Hz), 7.43–7.50 (2H, m), 7.91 (1H, dd,  $J = 7.6, 1.0$  Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{d}_6$ -acetone)  $\delta_{\text{C}}$  59.2, 74.6, 97.2, 105.2, 128.4, 129.0, 129.7, 139.3, 139.5, 148.1. All analytical data is in accordance with literature precedence.<sup>172</sup>

**(*E*)-3-Isobutoxyprop-2-en-1-ol (218n)**



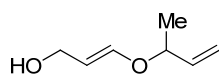
(*E*)-Methyl 3-isobutyloxyacrylate (1.38 g, 10.6 mmol) was reduced according to general procedure II (reaction time: 6 hours) to afford the product as a colourless oil (1.19 mg, 86%).  $^1\text{H}$  NMR (500MHz,  $\text{d}_6$ -acetone)  $\delta_{\text{H}}$  0.79 (6H, d,  $J = 6.7$  Hz), 1.77 (1H, oct,  $J = 6.7$  Hz), 3.15 (1H, t,  $J = 5.5$  Hz), 3.32 (2H, d,  $J = 6.7$  Hz), 3.81 (2H, ddd,  $J = 7.0, 5.5, 1.1$  Hz), 4.82 (1H, dt,  $J = 12.6, 7.0$  Hz), 6.35 (1H, d,  $J = 12.6$  Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{d}_6$ -acetone)  $\delta_{\text{C}}$  19.7, 29.3, 60.7, 76.5, 104.9, 150.3. All analytical data is in accordance with literature precedence.<sup>172</sup>

**(*E*)-3-(Cyclohexyloxy)prop-2-en-1-ol (218o)**



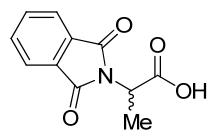
(*E*)-Methyl 3-(cyclohexyloxy)acrylate (838 mg, 4.55 mmol) was reduced according to general procedure II (reaction time: 4 hours) to afford the product as a yellow oil (525 mg, 74%). FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 3338, 2932, 2858, 1669, 1649; <sup>1</sup>H NMR (500MHz, d<sub>6</sub>-acetone)  $\delta_{\text{H}}$  1.21–1.56 (6H, m), 1.67–1.77 (2H, m), 1.79–1.91 (2H, m), 3.27 (1H, t,  $J$  = 5.6 Hz), 3.71–3.79 (1H, m), 3.91–3.97 (2H, m), 5.01 (1H, dt,  $J$  = 12.4, 7.2 Hz), 6.39 (1H, d,  $J$  = 12.4 Hz); <sup>13</sup>C NMR (125MHz, d<sub>6</sub>-acetone)  $\delta_{\text{C}}$  23.3, 25.3, 31.8, 59.3, 77.4, 105.1, 147.6.

**(*E*)-3-(But-3-en-2-yloxy)prop-2-en-1-ol (218p)**



(*E*)-Methyl 3-(but-3-en-2-yloxy)acrylate (2.27 g, 14.5 mmol) was reduced according to general procedure II (reaction time: 4 hours) to afford the product as a yellow oil (1.33 g, 72%). FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 3393, 2979, 2931, 2872, 1670, 1652; <sup>1</sup>H NMR (500MHz, d<sub>6</sub>-acetone)  $\delta_{\text{H}}$  1.26 (3H, d,  $J$  = 6.4 Hz), 3.33 (1H, t,  $J$  = 5.6 Hz), 3.93 (2H, app. t,  $J$  = 6.4 Hz), 4.35 (1H, app. p,  $J$  = 6.4 Hz), 5.03 (1H, dt,  $J$  = 12.4, 7.1 Hz), 5.13 (1H, dt,  $J$  = 10.6, 1.4 Hz), 5.24 (1H, dt,  $J$  = 17.3, 1.4 Hz), 5.82 (1H, ddd,  $J$  = 17.3, 10.6, 6.4 Hz), 6.37 (1H, d,  $J$  = 12.4 Hz); <sup>13</sup>C NMR (125MHz, d<sub>6</sub>-acetone)  $\delta_{\text{C}}$  20.2, 59.3, 76.7, 105.7, 114.9, 139.5, 147.4.

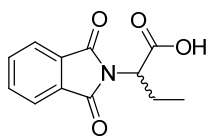
**2-(1,3-Dioxoisindolin-2-yl)propanoic acid (219b)**



DL-Alanine (1.10 g, 12.3 mmol) in toluene (50 mL), phthalic anhydride (1.84 g, 12.4 mmol) and triethylamine (1.74 mL, 12.3 mmol) were combined according to general procedure III (reaction time: 24 hours) to afford the title compound as a white powder (2.13 g, 79%). Mpt: 164–165 °C (lit.<sup>274</sup> 163 °C); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 3050, 2922, 2853, 1780, 1764, 1709; <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  1.66 (3H, d,  $J$  = 7.4 Hz), 4.98 (1H, q,  $J$  = 7.4 Hz), 7.62–7.71 (2H, m), 7.76–7.85 (2H, m), 10.02 (1H, bs); <sup>13</sup>C NMR

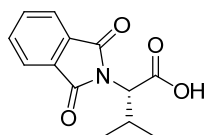
(75MHz, CDCl<sub>3</sub>)  $\delta_C$  15.4, 47.6, 124.0, 132.2, 134.6, 167.8, 176.0; HRMS (ESI, -ve)  $m/z$  calc. for C<sub>11</sub>H<sub>8</sub>NO<sub>4</sub> 218.0459, found 218.0452 (M-H)<sup>-</sup>.

### 2-(1,3-Dioxisoindolin-2-yl)butanoic acid (219c)

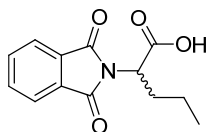


DL-2-Aminobutyric acid (2.76 g, 26.7 mmol) in toluene (100 mL), phthalic anhydride (4.00 g, 27.0 mmol) and triethylamine (3.74 mL, 26.7 mmol) were combined according to general procedure III (reaction time: 24 hours) to afford the title compound as an amorphous solid (4.77 g, 77%). Mpt: 95-96 °C (lit.<sup>275</sup> 95.5-96.5 °C); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 3050, 2976, 2881, 1776, 1713, 1613; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_H$  0.92 (3H, t,  $J$  = 7.4 Hz), 2.20–2.33 (2H, m), 4.81 (1H, dd,  $J$  = 8.6, 7.1 Hz), 7.67–7.77 (2H, m), 7.80–7.90 (2H, m), 11.47 (1H, bs); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_C$  10.9, 21.9, 53.5, 123.6, 131.6, 134.3, 167.7, 175.2; HRMS (ESI, +ve)  $m/z$  calc. for C<sub>12</sub>H<sub>11</sub>NO<sub>4</sub>Na 256.0586, found 256.0578 (M+Na)<sup>+</sup>.

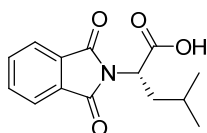
### (S)-2-(1,3-Dioxisoindolin-2-yl)-3-methylbutanoic acid (219d)



L-Valine (2.50 g, 21.3 mmol) in toluene (80 mL), phthalic anhydride (3.18 g, 21.5 mmol) and triethylamine (2.98 mL, 21.3 mmol) were combined according to general procedure III (reaction time: 24 hours) to afford the title compound as a white powder (4.93 g, 94%). Mpt: 112-114 °C (lit.<sup>276</sup> 112-113 °C);  $[\alpha]_D^{20}$  -38 ( $c$  1, MeOH), lit.<sup>276</sup> -51.4 ( $c$  1, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>)  $\delta_H$  0.92 (3H, d,  $J$  = 6.8 Hz), 1.17 (3H, d,  $J$  = 6.8 Hz), 2.68–2.85 (1H, m), 4.63 (1H, d,  $J$  = 8.5 Hz), 7.71–7.78 (2H, m), 7.84–7.91 (2H, m, ArH), 9.89 (1H, bs, CO<sub>2</sub>H); <sup>13</sup>C NMR (75MHz, CDCl<sub>3</sub>)  $\delta_C$  19.9, 21.3, 28.8, 58.0, 124.1, 132.0, 134.7, 168.1, 174.8. All analytical data is in accordance with literature precedence.<sup>276</sup>

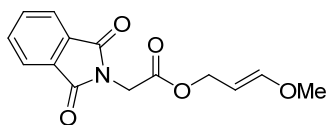
**2-(1,3-Dioxoisindolin-2-yl)pentanoic acid (219e)**

DL-Norvaline (5.00 g, 42.6 mmol) in toluene (180 mL), phthalic anhydride (6.36 g, 43 mmol) and triethylamine (5.96 mL, 42.6 mmol) were combined according to general procedure III (reaction time: 24 hours) to afford the title compound as a white powder (8.52 g, 81%). Mpt: 104-106 °C (lit.<sup>277</sup> 103-105°C); FTIR (film/cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 3031, 2964, 2870, 1775, 1699, 1612; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  0.94 (3H, t,  $J$  = 7.4 Hz), 1.29–1.41 (2H, m), 2.13–2.21 (1H, m), 2.27–2.37 (1H, m), 4.94 (1H, dd,  $J$  = 11.1, 4.7 Hz), 7.74 (2H, dd,  $J$  = 5.4, 3.1 Hz), 7.87 (2H, dd,  $J$  = 5.4, 3.1 Hz), 10.37 (1H, bs); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  13.3, 19.5, 30.3, 51.6, 123.6, 131.7, 134.2, 167.6, 175.4; HRMS (ESI, +ve)  $m/z$  calc. for C<sub>13</sub>H<sub>13</sub>NO<sub>4</sub>Na 270.0742, found 270.0740 (M+Na)<sup>+</sup>.

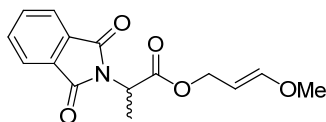
**(S)-2-(1,3-Dioxoisindolin-2-yl)-4-methylpentanoic acid (219f)**

L-Leucine (2.50 g, 19.1 mmol) in toluene (60 mL), phthalic anhydride (3.10 g, 21.0 mmol) and triethylamine (2.67 mL, 19.1 mmol) were combined according to general procedure III (reaction time: 24 hours) and recrystallised from EtOAc/Hexane to afford the title compound as white crystals (3.88 g, 78%). Mpt: 125-128 °C (lit.<sup>278</sup> 124-125 °C);  $[\alpha]_{\text{D}}^{20}$  -21 ( $c$  1, MeOH), lit.<sup>279</sup> -22.1 ( $c$  1, EtOH); FTIR (film/cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 3037, 2962, 2936, 2874, 1779, 1708, 1611; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  0.94 (3H, d,  $J$  = 6.6 Hz), 0.96 (3H, d,  $J$  = 6.6 Hz), 1.45–1.57 (1H, m), 1.96 (1H, ddd,  $J$  = 14.3, 10.8, 4.9 Hz), 2.38 (1H, ddd,  $J$  = 14.3, 10.8, 4.9 Hz), 5.01 (1H, dd,  $J$  = 11.6, 4.4 Hz), 5.68 (1H, bs), 7.72–7.77 (2H, m), 7.85–7.90 (1H, m); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  21.0, 23.0, 25.1, 37.0, 50.4, 123.6, 131.7, 134.2, 167.7, 175.1; HRMS (ESI, +ve)  $m/z$  calc. for C<sub>14</sub>H<sub>15</sub>NO<sub>4</sub>Na 284.0899, found 284.0897 (M+Na)<sup>+</sup>.

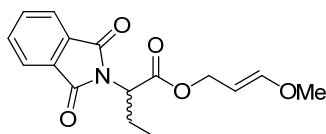


**(*E*)-3-Methoxyallyl 2-(1,3-dioxoisindolin-2-yl)acetate (220a)**

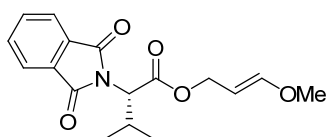
EDCI.HCl (433 mg, 2.26 mmol), triethylamine (319  $\mu$ l, 2.26 mmol), *N*-phthaloyl glycine (464 mg, 2.26 mmol), DMAP (5 mol%), DCM (30 mL) and (*E*)-3-(methoxy)prop-2-enol **218a** (100 mg, 1.13 mmol) were combined according to general procedure IV (reaction time: 6 hours), to afford the title compound as a white solid (230 mg, 74%). Mpt: 55–58 °C (lit.<sup>172</sup> 55–58 °C); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>H</sub> 3.58 (3H, s), 4.43 (2H, s), 4.61 (2H, d, *J* = 8.2 Hz), 4.92 (1H, dt, *J* = 12.6, 8.2 Hz), 6.65 (1H, d, *J* = 12.6 Hz), 7.73–7.77 (2H, m), 7.88–7.91 (2H, m); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>C</sub> 39.0, 56.2, 64.2, 96.3, 123.6, 132.1, 134.2, 154.0, 167.3, 167.5. All analytical data is in accordance with literature precedence.<sup>172</sup>

**(*E*)-3-Methoxyallyl 2-(1,3-dioxoisindolin-2-yl)propanoate (220b)**

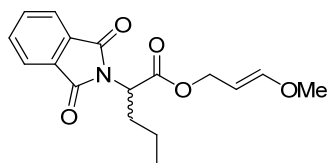
EDCI.HCl (479 mg, 2.50 mmol), triethylamine (353  $\mu$ l, 2.50 mmol), phthalyl-DL-alanine **219b** (547 mg, 2.50 mmol), DMAP (5 mol%), DCM (30 mL) and (*E*)-3-(methoxy)prop-2-enol **218a** (110 mg, 1.25 mmol) were combined according to the general procedure IV (reaction time: 6 hours), to afford the title compound as a colourless oil (298 mg, 82%); <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta$ <sub>H</sub> 1.69 (3H, d, *J* = 7.3 Hz), 3.55 (3H, s), 4.55–4.4.62 (2H, m), 4.85–4.92 (1H, m), 4.96 (1H, q, *J* = 7.3 Hz), 6.61 (1H, d, *J* = 12.6 Hz), 7.72–7.77 (2H, m), 7.85–7.89 (2H, m); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta$ <sub>C</sub> 15.3, 47.7, 56.1, 64.1, 96.5, 123.5, 132.0, 134.1, 153.7, 167.4, 169.7. All analytical data is in accordance with literature precedence.<sup>172</sup>

**(*E*)-3-Methoxyallyl 2-(1,3-dioxoisindolin-2-yl)butanoate (220c)**

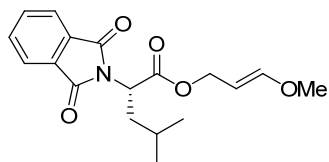
EDCI.HCl (870 mg, 4.54 mmol), triethylamine (634  $\mu$ l, 4.54 mmol), phthalyl-DL-2-aminobutyric acid **219c** (1.06 g, 4.54 mmol), DMAP (5 mol%), DCM (40 mL) and (*E*)-3-(methoxy)prop-2-enol **218a** (200 mg, 2.27 mmol) were combined according to general procedure IV (reaction time: 24 hours), to afford the title compound as a colourless oil (690 mg, 100%). FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2974, 2840, 1776, 1714, 1654;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  0.89 (3H, t,  $J = 7.5$  Hz), 2.17–2.28 (2H, m), 3.49 (3H, s), 4.53 (2H, d,  $J = 7.8$  Hz), 4.71 (1H, dd,  $J = 9.7, 6.2$  Hz), 4.83 (1H, dt,  $J = 12.6, 7.8$  Hz), 6.56 (1H, d,  $J = 12.6$  Hz), 7.68–7.73 (2H, m), 7.80–7.84 (2H, m);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  10.9, 22.1, 53.9, 56.0, 63.9, 96.5, 123.4, 131.8, 134.1, 153.6, 167.7, 169.3; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{16}\text{H}_{17}\text{NO}_5\text{Na}$  326.1004, found 326.0997 ( $\text{M}+\text{Na}$ ) $^{+}$ .

**(*S,E*)-3-Methoxyallyl 2-(1,3-dioxoisindolin-2-yl)-3-methylbutanoate (220d)**

EDCI.HCl (774 mg, 4.04 mmol), triethylamine (570  $\mu$ l, 4.04 mmol), phthalyl-L-valine **219d** (1.00 g, 4.04 mmol), DMAP (5 mol%), DCM (40 mL) and (*E*)-3-(methoxy)prop-2-enol **218a** (178 mg, 2.02 mmol) were combined according to general procedure IV (reaction time: 24 hours), to afford the title compound as a colourless oil (600 mg, 94%). FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2967, 2935, 1774, 1715, 1715, 1655;  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  0.84 (3H, d,  $J = 6.8$  Hz), 1.07 (3H, d,  $J = 6.7$  Hz), 2.61–2.77 (1H, m), 3.45 (3H, s), 4.41–4.56 (3H, m), 4.79 (1H, dt,  $J = 12.6, 7.8$  Hz), 6.51 (1H, d,  $J = 12.6$  Hz), 7.61–7.72 (2H, m), 7.74–7.84 (2H, m);  $^{13}\text{C}$  NMR (75MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  19.9, 21.3, 29.0, 56.5, 58.3, 64.1, 97.0, 123.9, 132.2, 134.5, 153.9, 168.2, 169.2; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{17}\text{H}_{19}\text{NO}_5\text{Na}$  340.1161, found 340.1157 ( $\text{M}+\text{Na}$ ) $^{+}$ .

**(*E*)-3-Methoxyallyl 2-(1,3-dioxoisindolin-2-yl)pentanoate (220e)**

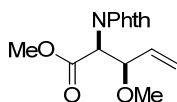
EDCi.HCl (1.30 g, 6.80 mmol), triethylamine (950  $\mu$ l, 6.80 mmol), phthalyl-DL-norvaline **219e** (841 mg, 3.40 mmol), DMAP (5 mol%), DCM (60 mL) and (*E*)-3-(methoxy)prop-2-enol **218a** (300 mg, 3.40 mmol) were combined according to general procedure IV (reaction time: 24 hours), to afford the title compound as a colourless oil (746 mg, 70%). FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2966, 1776, 1715, 1655;  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  0.94 (3H, t,  $J = 7.3$  Hz), 1.23–1.42 (2H, m), 2.09–2.37 (2H, m), 3.55 (3H, s), 4.58 (2H, d,  $J = 8.0$  Hz), 4.81–4.96 (2H, m), 6.60 (1H, d,  $J = 12.6$  Hz), 7.71–7.7.79 (2H, m), 7.84–7.91 (2H, m);  $^{13}\text{C}$  NMR (75MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  13.8, 20.0, 31.0, 52.6, 56.3, 64.4, 97.0, 123.9, 132.3, 134.5, 154.0, 168.1, 169.9; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{17}\text{H}_{19}\text{NO}_5\text{Na}$  340.1161, found 340.1155 ( $\text{M}+\text{Na}$ ) $^{+}$ .

**(*S,E*)-3-Methoxyallyl 2-(1,3-dioxoisindolin-2-yl)-4-methylpentanoate (220f)**

EDCi.HCl (734 mg, 3.83 mmol), triethylamine (535  $\mu$ l, 3.83 mmol), phthalyl-L-leucine **219f** (500 mg, 1.91 mmol), DMAP (5 mol%), DCM (40 mL) and (*E*)-3-(methoxy)prop-2-enol **218a** (1.91 mmol, 169 mg) were combined according to general procedure IV (reaction time: 24 hours), to afford the title product as a colourless oil (475 mg, 75%). FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2960, 5874, 1776, 1714, 1655;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  0.94 (3H, d,  $J = 6.6$  Hz), 0.96 (3H, d,  $J = 6.6$  Hz), 1.45–1.55 (1H, m), 1.96 (1H, ddd,  $J = 14.3, 11.0, 4.1$  Hz), 2.35 (1H, ddd,  $J = 14.3, 11.0, 4.1$  Hz), 3.56 (3H, s), 4.58 (2H, d,  $J = 7.8$  Hz), 4.85–4.90 (1H, m), 4.91–4.96 (1H, m), 6.61 (1H, d,  $J = 12.6$  Hz), 7.73–7.77 (2H, m), 7.85–7.90 (2H, m);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  21.0, 23.2, 25.1, 37.2,

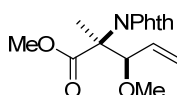
51.0, 56.1, 64.1, 96.6, 123.5, 131.9, 134.1, 153.7, 167.8, 169.8; HRMS (ESI, +ve)  $m/z$  calcd. for  $C_{18}H_{21}NO_5Na$  354.1317, found 354.1324 ( $M+Na$ )<sup>+</sup>.

**(±)-(syn)-Methyl 2-(1,3-dioxoisindolin-2-yl)-3-methoxypent-4-enoate (221a)**



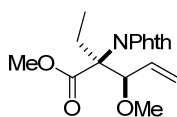
To a solution of (*E*)-3-methoxyallyl 2-(1,3-dioxoisindolin-2-yl)acetate **220a** (280 mg, 1.03 mmol, 1.0 eq) in THF (2.8 mL) at -95 °C was added TMSCl (171 μL, 1.34 mmol, 1.3 eq). After 10 mins LHMDS (1M, 1.34 mL, 1.34 mmol, 1.3 eq) was added *via* syringe pump at an addition rate of 3 mL min<sup>-1</sup> and reaction mixture allowed to warm to room temperature after a period of 30 mins, and stirred for 90 minutes. The reaction was quenched by the addition of 1N HCl and brine solution (1:1, 5 mL) and extracted with DCM (3 × 15 mL), EtOAc (1 × 15 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to afford the crude acid. Treatment with diazomethane according to general procedure VIII and purification by flash chromatography (4:1 Pet/EtOAc + 1% NEt<sub>3</sub>) affords the methyl ester as a colourless oil. (220 mg, 74%, dr 11:1). <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>) δ<sub>H</sub> major diastereomer 3.15 (3H, s), 3.65 (3H, s), 4.47 (1H, app. t, *J* = 8.6 Hz), 4.81 (1H, d, *J* = 8.6 Hz), 5.32 (1H, dt, *J* = 10.1, 1.3 Hz), 5.37 (1H, dt, *J* = 17.1, 1.3 Hz), 5.79 (1H, ddd, *J* = 17.1, 10.1, 1.3 Hz), 7.63–7.72 (2H, m), 7.75–7.85 (2H, m); δ<sub>H</sub> minor diastereomer 3.33 (3H, s), 3.69 (3H, s), 4.61 (1H, t, *J* = 9.1 Hz), 4.94 (1H, d, *J* = 9.1 Hz), 5.10 (1H, dt, *J* = 10.7, 1.2 Hz), 5.20 (1H, dt, *J* = 17.7, 1.2 Hz), 5.53 (1H, ddd, *J* = 17.7, 10.7, 6.8 Hz), 7.72 – 7.75 (2H, m), 7.84 – 7.89 (2H, m); <sup>13</sup>C NMR (75MHz, CDCl<sub>3</sub>) δ<sub>C</sub> major diastereomer 52.9, 56.1, 57.1, 78.6, 120.3, 124.0, 132.3, 134.6, 135.4, 167.9, 168.2; δ<sub>C</sub> minor diastereomer 53.1, 54.0, 57.3, 80.5, 121.2, 124.0, 132.5, 134.2, 134.8, 167.8, 168.1. All analytical data is in accordance with literature precedence.<sup>172</sup>

**(±)-(syn)-Methyl 2-(1,3-dioxoisindolin-2-yl)-3-methoxy-2-methylpent-4-enoate (221b)**



To a solution of (*E*)-3-methoxyallyl 2-(1,3-dioxoisindolin-2-yl)propanoate **220b** (220 mg, 0.74 mmol, 1.0 eq) in THF (2.2 mL) at -95 °C was added TMSCl (122  $\mu$ L, 0.96 mmol, 1.3 eq). After 10 mins LHMDS (1M, 960  $\mu$ L, 0.96 mmol, 1.3 eq) was added *via* syringe pump at an addition rate of 3 mL min<sup>-1</sup> and reaction mixture allowed to warm to room temperature after a period of 30 mins, and stirred for 90 minutes. The reaction was quenched by the addition of 1N HCl and brine solution (1:1, 5 mL) and extracted with DCM (3  $\times$  15 mL), EtOAc (1  $\times$  15 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to afford the crude acid. Treatment with diazomethane according to general procedure VIII and purification by flash chromatography (6:1 Pet/EtOAc + 1% NEt<sub>3</sub>) affords the methyl ester as a colourless oil. (160 mg, 71%, dr 24:1). <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta$ <sub>H</sub> major diastereomer 1.84 (3H, s), 3.27 (3H, s), 3.75 (3H, s), 4.48 (1H, dt, *J* = 7.7, 0.6 Hz), 5.31–5.38 (2H, m), 5.99 (1H, ddd, *J* = 17.1, 10.3, 7.7 Hz), 7.70–7.74 (2H, m), 7.79–7.83 (2H, m);  $\delta$ <sub>H</sub> minor diastereomer 1.79 (3H, s), 3.32 (3H, s), 3.77 (3H, s), 4.60 (1H, dt, *J* = 8.0, 0.8 Hz), 5.26–5.30 (2H, m), 5.73 (1H, ddd, *J* = 17.1, 10.3, 8.0 Hz), 7.70–7.74 (2H, m), 7.79–7.83 (2H, m); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta$ <sub>C</sub> major diastereomer 19.3, 52.4, 57.2, 65.6, 83.8, 120.5, 123.2, 131.7, 133.5, 134.0, 168.2, 170.6;  $\delta$ <sub>C</sub> minor diastereomer 19.3, 52.5, 56.8, 65.2, 83.1, 121.1, 123.4, 131.9, 133.0, 134.2, 168.3, 169.7. All analytical data is in accordance with literature precedence.<sup>172</sup>

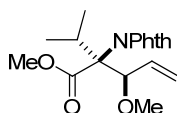
**(±)-(syn)-Methyl 2-(1,3-dioxoisindolin-2-yl)-3-methoxy-2-ethylpent-4-enoate (221c)**



To a solution of (*E*)-3-methoxyallyl 2-(1,3-dioxoisindolin-2-yl)butanoate **220c** (50 mg, 0.165 mmol, 1.0 eq) in THF (0.5 mL) at -78 °C was added TMSCl (42  $\mu$ L, 0.330 mmol, 2.0 eq). After 10 mins LHMDS (1M, 330  $\mu$ L, 0.330 mmol, 2.0 eq) was added and reaction mixture allowed to warm to room temperature after 30 mins, and stirred for 18 hours. The reaction was quenched by the addition of 1N HCl and brine solution (1:1, 5 mL) and extracted with DCM (3  $\times$  15 mL), EtOAc (1  $\times$  15 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to afford the crude acid. Treatment with diazomethane according to general procedure VIII and purification by flash chromatography (8:1 Pet/EtOAc +

1% NEt<sub>3</sub>) affords the methyl ester as a colourless oil (10.4 mg, 20%, dr 2.7:1). FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2997, 2957, 2829, 1784, 1753, 1718; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  major diastereomer 0.93 (3H, t,  $J$  = 7.4 Hz), 2.25–2.35 (1H, m), 2.60 (1H, dq,  $J$  = 14.6, 7.4 Hz), 3.31 (3H, s), 3.80 (3H, s), 4.58 (1H, d,  $J$  = 8.2 Hz), 5.31–5.38 (2H, m), 5.98 (1H, app. dt,  $J$  = 17.3 Hz, 8.2 Hz), 7.70–7.75 (2H, m), 7.79–7.84 (2H, m);  $\delta_{\text{H}}$  minor diastereomer 0.93 (3H, t,  $J$  = 7.4 Hz), 2.13–2.22 (1H, m), 2.49 (1H, dq,  $J$  = 14.6, 7.4 Hz), 3.31 (3H, s), 3.80 (3H, s), 4.89 (1H, d,  $J$  = 8.2 Hz), 5.32–5.41 (2H, m), 5.67–5.78 (1H, m), 7.69–7.74 (2H, m), 7.75–7.87 (2H, m); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  major diastereomer 9.0, 26.5, 52.1, 57.3, 69.0, 84.1, 120.5, 123.2, 131.5, 133.5, 134.0, 168.4, 169.4; HRMS (ESI, +ve)  $m/z$  calcd. for C<sub>17</sub>H<sub>19</sub>NO<sub>5</sub>Na 340.1161, found: 340.1158 (M+Na)<sup>+</sup>.

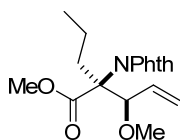
**(±)-(syn)-Methyl 2-(1,3-dioxoisindolin-2-yl)-2-isopropyl-3-methoxypent-4-enoate (221d)**



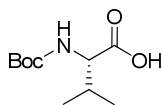
To a solution of (*S,E*)-3-methoxyallyl 2-(1,3-dioxoisindolin-2-yl)-3-methylbutanoate **220d** (102 mg, 0.320 mmol, 1.0 eq) in THF (1.0 mL) at -95 C° was added TMSCl (54  $\mu$ L, 0.420 mmol, 1.3 eq). After 10 mins LHMDS (1M, 420  $\mu$ L, 0.420 mmol, 1.3 eq) was added and reaction mixture allowed to warm to room temperature after a period of 30 mins, and stirred for 90 minutes. LHMDS (0.320 mmol, 320  $\mu$ L, 1.0 eq) was added and the reaction mixture stirred for 18 hours. The reaction was quenched by the addition of 1N HCl and brine solution (1:1, 5 mL) and extracted with DCM (3  $\times$  15 mL), EtOAc (1  $\times$  15 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to afford the crude acid. Treatment with diazomethane according to general procedure VIII and purification by flash chromatography (8:1 Pet/EtOAc + 1% NEt<sub>3</sub>) affords the methyl ester as a colourless oil (12 mg, 11%, dr undeterminable). FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2993, 2957, 2822, 1779, 1747, 1720; <sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  0.93 (3H, d,  $J$  = 6.9 Hz), 1.04 (3H, d,  $J$  = 6.9 Hz), 1.81–1.89 (1H, m), 3.27 (3H, s), 3.80 (3H, s), 4.61 (1H, d,  $J$  = 8.8 Hz), 5.24–5.36 (2H, m), 5.77–5.94 (1H, m), 7.65–7.83 (4H, m); <sup>13</sup>C NMR (75MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  18.5, 19.2, 30.1, 52.2, 57.3, 72.1, 84.9, 120.8, 123.6, 132.0, 133.8, 134.3,

168.9, 169.3; HRMS (ESI, +ve)  $m/z$  calcd. for  $C_{18}H_{21}NO_5Na$  354.1317, found: 354.1319 ( $M+Na$ )<sup>+</sup>.

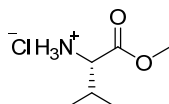
**(±)-(syn)-Methyl 2-(1,3-dioxoisindolin-2-yl)-3-methoxy-2-propylpent-4-enoate (221e)**



To a solution of (*E*)-3-methoxyallyl 2-(1,3-dioxoisindolin-2-yl)pentanoate **220e** (50 mg, 0.160 mmol, 1.0 eq) in THF (0.5 mL) at -78 °C was added TMSCl (41 µL, 0.320 mmol, 2.0 eq). After 10 mins LHMDS (1M, 320 µl, 0.320 mmol, 2.0 eq) was added *via* syringe pump at an addition rate of 3 mL min<sup>-1</sup> and reaction mixture allowed to warm to room temperature after a period of 30 mins, and stirred for 18 hours. The reaction was quenched by the addition of 1N HCl and brine solution (1:1, 5 mL) and extracted with DCM (3 × 15 mL), EtOAc (1 × 15 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to afford the crude acid. Treatment with diazomethane according to general procedure VIII and purification by flash chromatography (8:1 Pet/EtOAc + 1% NEt<sub>3</sub>) affords the methyl ester as a colourless oil. (24 mg, 45%, dr 2:1). FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2934, 1779, 1743, 1715; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_H$  major diastereomer 0.91 (3H, t,  $J$  = 7.3 Hz), 1.13–1.23 (1H, m), 1.40–1.48 (1H, m), 2.19–2.27 (1H, m), 2.42–2.50 (1H, m), 3.29 (3H, s), 3.79 (3H, s), 4.57 (1H, d,  $J$  = 8.2 Hz), 5.30–5.37 (2H, m), 5.93–6.02 (1H, m), 7.69–7.74 (2H, m), 7.78–7.82 (2H, m);  $\delta_H$  minor diastereomer 0.90 (3H, t,  $J$  = 7.3 Hz), 1.25–1.38 (2H, m), 2.06–2.16 (1H, m), 2.33–2.42 (1H, m), 3.31 (3H, s), 3.78 (3H, s), 4.89 (1H, d,  $J$  = 8.1 Hz), 5.34–5.40 (2H, m), 5.66–5.74 (1H, m), 7.69–7.74 (2H, m), 7.78–7.82 (2H, m); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_C$  major diastereomer 14.2, 21.0, 35.5, 52.1, 57.3, 68.5, 84.3, 100.5, 123.2, 131.5, 133.6, 134.0, 168.3, 169.5;  $\delta_C$  minor diastereomer 14.2, 17.3, 34.9, 52.4, 56.5, 69.1, 81.4, 120.9, 123.1, 131.7, 132.9, 134.0, 168.7, 169.6; HRMS (ESI, +ve)  $m/z$  calcd. for  $C_{18}H_{21}NO_5Na$  354.1317, found: 354.1318 ( $M+Na$ )<sup>+</sup>.

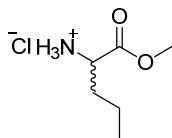
**(S)-2-(tert-Butoxycarbonylamino)-3-methylbutanoic acid (226d)**

To a solution of L-valine (1.00 g, 8.54 mmol, 1.0 eq) and 1N sodium hydroxide (10.3 mL, 10.3 mmol, 1.2 eq) in dioxane (20 mL) was added  $\text{Boc}_2\text{O}$  (1.86 g, 8.54 mmol, 1.0 eq) in dioxane (10 mL) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 18 hours. Reaction mixture was acidified with 1N HCl and extracted with EtOAc ( $3 \times 50$  mL), washed with 1N HCl ( $1 \times 50$  mL), dried and concentrated *in vacuo* to afford the title compound as white crystals (1.86 g, 100%). Mpt: 78–80 °C (lit.<sup>280</sup> 77–78 °C);  $[\alpha]_{\text{D}}^{20}$  -6 (*c* 1, acetic acid), lit.<sup>280</sup> -5.8 (*c* 1, acetic acid);  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  0.87 (3H, d,  $J = 6.8$  Hz), 0.94 (3H, d,  $J = 6.8$  Hz), 1.38 (9H, s), 1.99–2.22 (1H, m), 4.10–4.25 (1H, m), 4.94 (1H, app. d,  $J = 8.7$  Hz), 8.61 (1H, bs);  $^{13}\text{C}$  NMR (75MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  17.9, 19.4, 27.8, 28.7, 31.4, 67.5, 156.9, 177.3. All analytical data is in accordance with literature precedence.<sup>281</sup>

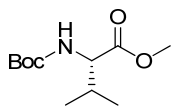
**L-Valine methyl ester hydrochloride (228d)**

L-Valine (5.00 g, 42.7 mmol) in MeOH (350 mL) and thionyl chloride (20.2 mL, 278 mmol, 7.0 eq) were combined according to general procedure V to afford L-valine methyl ester hydrochloride as a white powder (6.40 g, 90%). Mpt: 170–173 °C (lit.<sup>282</sup> 173–174 °C);  $[\alpha]_{\text{D}}^{20}$  +24 (*c* 1, MeOH), lit.<sup>283</sup> +24.2 (*c* 1, MeOH);  $^1\text{H}$  NMR (500MHz,  $\text{D}_2\text{O}$ )  $\delta$ : 0.96 (6H, app t,  $J = 6.9$  Hz), 2.23–2.33 (1H, m), 3.79 (3H, s), 3.97 (1H, d,  $J = 4.7$  Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{D}_2\text{O}$ )  $\delta$ : 16.9, 17.2, 29.3, 53.4, 58.4, 170.4. All analytical data is in accordance with literature precedence.<sup>283</sup>

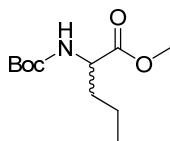


**DL-Norvaline methyl ester hydrochloride (228e)**

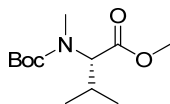
DL-Norvaline (6.00 g, 51.2 mmol) in MeOH (350 mL) and thionyl chloride (26.2 mL, 359 mmol, 7.0 eq) were combined according to general procedure V to afford DL-norvaline methyl ester hydrochloride as a white powder (8.55 g, 100%). Mpt: 109 -112 °C (lit.<sup>284</sup> 114-115 °C); FTIR (film/cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 3000, 2956, 2875, 1751; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  0.87 (3H, t,  $J$  = 7.3 Hz), 1.27–1.44 (2H, m), 1.77–1.94 (2H, m), 3.77 (3H, s), 4.08 (1H, t,  $J$  = 6.5 Hz); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  12.7, 17.7, 31.7, 52.7, 53.5, 171.0; HRMS (ESI, +ve)  $m/z$  calcd. for C<sub>6</sub>H<sub>14</sub>NO<sub>2</sub> 132.1025, found: 132.1023 (M+H)<sup>+</sup>.

**(S)-Methyl 2-(tert-butoxycarbonylamino)-3-methylbutanoate (229d)**

To a solution of L-valine methyl ester hydrochloride **228d** (6.38 g, 38.2 mmol, 1.0 eq) and triethylamine (16 mL, 114.6 mmol, 3.0 eq) in THF (130 mL) was added Boc<sub>2</sub>O (10.0 g, 45.8 mmol, 1.2 eq) in THF (20 mL). Reaction mixture was allowed to stir at room temperature for 4 days. The solution was then concentrated *in vacuo*. Purification by flash chromatography (4:1 Pet/EtOAc) affords the title compound as a colourless oil (8.53 g, 97%).  $[\alpha]_{\text{D}}^{20}$  -22.5 ( $c$  2, MeOH), lit.<sup>285</sup> -21.9 ( $c$  2.2, MeOH); <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  0.88 (3H, d,  $J$  = 6.9 Hz), 0.95 (3H, d,  $J$  = 6.9 Hz), 1.44 (9H, s), 2.02–2.20 (1H, m), 3.73 (3H, s), 4.15–4.27 (1H, m), 4.90–5.09 (1H, m); <sup>13</sup>C NMR (75MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  18.0, 19.4, 28.7, 31.7, 52.4, 58.9, 80.2, 156.0, 173.3. All analytical data is in accordance with literature precedence.<sup>285</sup>

**Methyl 2-(*tert*-butoxycarbonylamino)pentanoate (229e)**

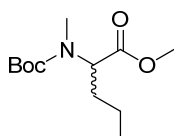
To a solution of DL-norvaline methyl ester hydrochloride **228e** (8.35 g, 50.0 mmol, 1.0 eq) and triethylamine (17.8 mL, 150 mmol, 3.0 eq) in THF (130 mL) was added  $\text{Boc}_2\text{O}$  (13.1 g, 60.0 mmol, 1.2 eq) in THF (20 mL). Reaction mixture was allowed to stir at room temperature for 4 days. The solution was then concentrated *in vacuo*. Purification by flash chromatography (4:1 Pet/EtOAc) affords the title compound as a colourless oil (11.56 g, 100%). FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 3361, 2962, 1741, 1716;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  0.93 (3H, t,  $J = 7.3$  Hz), 1.30–1.42 (2H, m), 1.45 (9H, s), 1.55–1.81 (2H, m), 3.73 (3H, s), 4.24–4.34 (1H, m), 4.93–5.07 (1H, m);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  13.6, 18.6, 27.4, 28.3, 34.9, 52.1, 53.2, 155.4, 173.5; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{11}\text{H}_{21}\text{NO}_4\text{Na}$  254.1368, found: 254.1350 ( $\text{M}+\text{Na}$ ) $^+$ .

**(*S*)-Methyl 2-(*tert*-butoxycarbonyl(methyl)amino)-3-methylbutanoate (230d)**

To a solution of *N*-Boc-L-valine methyl ester **229d** (1.61 g, 6.96 mmol, 1.0 eq) and methyl iodide (650  $\mu\text{L}$ , 10.4 mmol, 1.5 eq) in DMF (40 mL) at 0  $^{\circ}\text{C}$  was added sodium hydride (334 mg, 13.9 mmol, 2.0 eq) and the reaction mixture allowed to stir at room temperature overnight. The solution was then quenched with  $\text{NH}_4\text{Cl}$  (sat) (50 mL) and extracted with EtOAc ( $3 \times 50$  mL), washed with brine ( $1 \times 50$  mL), dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo*. Purification by flash chromatography (6:1 Pet/EtOAc) affords the title compound as a colourless oil (1.16 g, 68 %).  $[\alpha]_{\text{D}}^{20}$  -87.5 ( $c$  2, MeOH), lit.<sup>286</sup> -88.1 ( $c$  1.1, MeOH);  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  rotamer A 0.89 (3H, d,  $J = 5.8$  Hz), 0.96 (3H, d,  $J = 6.6$  Hz), 1.46 (9H, s), 2.12–2.24 (1H, m), 2.83 (3H, app. d,  $J = 15.2$  Hz), 3.70 (3H, s), 4.09 (1H, d,  $J = 10.3$  Hz);  $\delta_{\text{H}}$  rotamer B 0.89 (3H, d,  $J = 5.8$  Hz), 0.96 (3H, d,  $J = 6.6$  Hz), 1.46 (9H, s), 2.12–2.24 (1H, m), 2.83 (3H, app. d,  $J = 15.2$

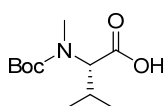
Hz), 3.70 (3H, s), 4.46 (1H, d,  $J = 10.6$  Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  rotamer A 18.7, 19.7, 28.3, 29.7, 30.3, 51.6, 63.0, 80.0, 155.6, 171.6;  $\delta_{\text{C}}$  rotamer B 19.0, 20.0, 27.9, 28.3, 30.7, 51.6, 65.0, 80.2, 156.3, 172.1. All analytical data is in accordance with literature precedence.<sup>286</sup>

### Methyl 2-(*tert*-butoxycarbonyl(methyl)amino)pentanoate (**230e**)



To a solution of *N*-Boc-DL-norvaline methyl ester **229e** (1.11 g, 4.80 mmol, 1.0 eq) and methyl iodide (448  $\mu\text{L}$ , 7.20 mmol, 1.5 eq) in DMF (60 mL) at 0 °C was added sodium hydride (230 mg, 9.60 mmol, 2.0 eq) and the reaction mixture allowed to stir at room temperature overnight. The solution was then quenched with  $\text{NH}_4\text{Cl}$  (sat) (50 mL) and extracted with EtOAc ( $3 \times 50$  mL), washed with brine ( $1 \times 50$  mL), dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo*. Purification by flash chromatography (6:1 Pet/EtOAc) affords the title compound as a colourless oil (1.01 g, 86 %). FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2964, 2939, 2878, 1744, 1696;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  rotamer A 0.95 (3H, t,  $J = 7.2$  Hz), 1.25–1.41 (2H, m), 1.45 (9H, s), 1.61–1.93 (2H, m), 2.78 (3H, s), 3.71 (3H, s), 4.41–4.49 (1H, m);  $\delta_{\text{H}}$  rotamer B 0.95 (3H, t,  $J = 7.2$  Hz), 1.25–1.41 (2H, m), 1.47 (9H, s), 1.61–1.93 (2H, m), 2.83 (3H, s), 3.71 (3H, s), 4.75–4.83 (1H, m);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  rotamer A 13.6, 19.2, 28.3, 30.3, 30.9, 52.0, 57.3, 79.9, 156.4, 172.6;  $\delta_{\text{C}}$  rotamer B 13.6, 19.3, 28.3, 30.8, 31.2, 52.0, 58.8, 80.2, 156.4, 172.8; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{12}\text{H}_{23}\text{NO}_4\text{Na}$  268.1525, found: 268.1501 ( $\text{M}+\text{Na}$ )<sup>+</sup>.

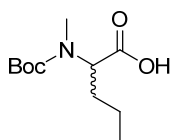
### (*S*)-2-(*tert*-Butoxycarbonyl(methyl)amino)-3-methylbutanoic acid (**227d**)



*N*-Boc-*N*-Me-*L*-valine methyl ester **230d** (990 mg, 4.04 mmol, 1.0 eq) was added to a solution of  $\text{LiOH}\cdot\text{H}_2\text{O}$  (509 mg, 12.1 mmol, 3.0 eq) in THF/ $\text{H}_2\text{O}$  (30 mL, 1:1) at 0 °C

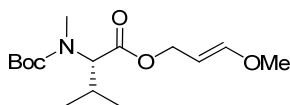
and allowed to stir for 5 hours. The reaction mixture was acidified to pH 4 with glacial acetic acid and extracted with EtOAc. The organics were washed with brine, dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to afford the title compound as a colourless oil without the need for further purification (890 mg, 96%).  $[\alpha]_{\text{D}}^{20}$  -89 (*c* 1, MeOH), lit.<sup>287</sup> -85 (*c* 0.5, EtOH);  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  0.91 (3H, d,  $J$  = 6.7 Hz), 1.02 (3H, d,  $J$  = 6.7 Hz), 1.47 (9H, s), 2.14–2.39 (1H, m), 2.87 (3H, s), 4.04–4.17 (1H, m), 9.10 (1H, bs);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  19.3, 27.4, 28.5, 32.0, 72.2, 79.9, 155.6, 175.8. All analytical data is in accordance with literature precedence.<sup>287</sup>

### 2-(*tert*-Butoxycarbonyl(methyl)amino)pentanoic acid (227e)



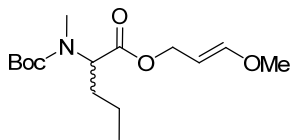
*N*-Boc-*N*-Me-DL-norvaline methyl ester **230e** (967 mg, 3.94 mmol, 1.0 eq) was added to a solution of  $\text{LiOH}\cdot\text{H}_2\text{O}$  (496 mg, 11.8 mmol, 3.0 eq) in THF/ $\text{H}_2\text{O}$  (20 mL, 1:1) at 0 °C and allowed to stir for 5 hours. The reaction mixture was acidified to pH 4 with glacial acetic acid and extracted with EtOAc. The organics were washed with brine, dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to afford the title compound as a colourless oil without the need for further purification (911 mg, 100%). FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 3080, 2965, 2935, 2877, 1698, 1673;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  rotamer A 0.97 (3H, t,  $J$  = 7.4 Hz), 1.28–1.42 (2H, m), 1.46 (9H, s), 1.69–1.83 (2H, m), 2.82 (3H, s), 4.51 (1H, m);  $\delta_{\text{H}}$  rotamer B 0.97 (3H, t,  $J$  = 7.4 Hz), 1.28–1.42 (2H, m), 1.48 (9H, s), 1.84–1.99 (2H, m), 2.85 (3H, s), 4.72 (1H, m);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  rotamer A 13.6, 19.4, 28.3, 30.5, 30.9, 58.1, 80.6, 155.7, 176.8;  $\delta_{\text{C}}$  rotamer B 13.6, 20.7, 28.3, 30.5, 31.0, 58.6, 80.6, 156.8, 176.8; HRMS (ESI, -ve)  $m/z$  calcd. for  $\text{C}_{11}\text{H}_{20}\text{NO}_4$  230.2813, found: 230.1373 ( $\text{M}-\text{H}$ ) $^-$ .

**(*S,E*)-3-Methoxyallyl 2-(*tert*-butoxycarbonyl(methyl)amino)-3-methylbutanoate (231d)**



EDCi.HCl (738 mg, 3.85 mmol), triethylamine (538  $\mu$ l, 3.85 mmol), (*S*)-2-(*tert*-butoxycarbonyl(methyl)amino)-3-methylbutanoic acid **227d** (890 mg, 3.85 mmol), DMAP (5 mol%), DCM (40 mL) and (*E*)-3-(methoxy)prop-2-enol **218a** (170 mg, 1.92 mmol) were combined according to general procedure IV (reaction time: 24 hours), to afford the title compound as a yellow oil (443 mg, 77%). FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2967, 2936, 1785, 1733, 1694, 1655;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  rotamer A 0.90 (3H, d,  $J = 6.5$  Hz), 0.98 (3H, d,  $J = 6.5$  Hz), 1.45 (9H, s), 2.13-2.31 (1H, m), 2.82 (3H, s), 3.57 (3H, s), 4.09 (1H, d,  $J = 10.5$  Hz), 4.54 (2H, d,  $J = 7.7$  Hz), 4.92 (1H, dt,  $J = 12.6, 7.7$  Hz), 6.64 (1H, d,  $J = 12.6$  Hz);  $\delta_{\text{H}}$  rotamer B 0.90 (3H, d,  $J = 6.5$  Hz), 0.98 (3H, d,  $J = 6.5$  Hz), 1.45 (9H, s), 2.13-2.31 (1H, m), 2.86 (3H, s), 3.59 (3H, s), 4.43 (1H, d,  $J = 10.5$  Hz), 4.54 (2H, d,  $J = 7.7$  Hz), 4.92 (1H, dt,  $J = 12.6, 7.7$  Hz), 6.64 (1H, d,  $J = 12.6$  Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  rotamer A 16.2, 18.8, 19.7, 27.8, 28.4, 56.1, 62.6, 63.3, 65.1, 66.2, 96.9, 153.2, 171.1;  $\delta_{\text{C}}$  rotamer B 17.3, 19.1, 20.0, 27.8, 28.4, 56.1, 62.8, 63.3, 65.1, 66.2, 96.9, 153.5, 171.1; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{15}\text{H}_{27}\text{NO}_5\text{Na}$  324.1787, found: 324.1785 ( $\text{M}+\text{Na}$ ) $^+$ .

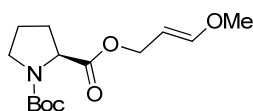
**(*E*)-3-Methoxyallyl 2-(*tert*-butoxycarbonyl(methyl)amino)pentanoate (231e)**



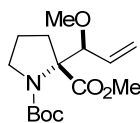
EDCi.HCl (755 mg, 3.94 mmol), triethylamine (550  $\mu$ L, 3.94 mmol), 2-(*tert*-butoxycarbonyl(methyl)amino)pentanoic acid **227e** (911 mg, 3.94 mmol), DMAP (5 mol%), DCM (40 mL) and (*E*)-3-(methoxy)prop-2-enol **218a** (174 mg, 1.97 mmol) were combined according to the general procedure IV (reaction time: 24 hours), to afford the title compound as a yellow oil (253 mg, 43%). FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2968,

2939, 1788, 1732, 1689, 1656;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H rotamer A}}$  0.90–0.96 (3H, m), 1.25–1.42 (2H, m), 1.48 (9H, s), 1.81–1.97 (2H, m), 2.83 (3H, s), 3.59 (3H, s), 4.55 (2H, d,  $J = 7.7$  Hz), 4.76 (1H, dd,  $J = 10.9, 4.8$  Hz), 4.88 (1H, m), 6.65 (1H, d,  $J = 6.5$  Hz);  $\delta_{\text{H rotamer B}}$  0.90–0.96 (3H, m), 1.25–1.42 (2H, m), 1.45 (9H, s), 1.64–1.80 (2H, m), 2.79 (3H, s), 3.58 (3H, s), 4.44 (1H, dd,  $J = 10.9, 4.8$  Hz), 4.51 (2H, d,  $J = 7.7$  Hz), 4.88 (1H, m), 6.63 (1H, d,  $J = 6.5$  Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C rotamer A}}$  13.5, 19.2, 28.2, 30.3, 30.6, 55.9, 62.9, 77.3, 79.7, 96.7, 153.2, 155.6, 171.8;  $\delta_{\text{C rotamer B}}$  13.5, 19.3, 28.2, 30.4, 31.0, 56.0, 63.0, 77.3, 80.0, 96.8, 153.4, 156.3, 172.1; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{15}\text{H}_{27}\text{NO}_5\text{Na}$  324.1787, found: 324.1773 ( $\text{M}+\text{Na}$ ) $^+$ .

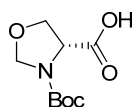
**(*S,E*)-1-*tert*-Butyl 2-(3-methoxyallyl) pyrrolidine-1,2-dicarboxylate (233)**



EDCI.HCl (1.52 g, 7.95 mmol), triethylamine (1.10 ml, 7.95 mmol), Boc-L-Pro-OH (1.71 g, 7.95 mmol), catalytic DMAP and (*E*)-3-(methoxy)prop-2-enol **218a** (350 mg, 3.97 mmol) were combined according to general procedure 3. Purification was achieved by flash chromatography (4:1 Pet/EtOAc + 1%  $\text{NEt}_3$ ) to afford the title compound as a colourless oil (736 mg, 65%).  $[\alpha]_{\text{D}}^{20}$  -89 ( $c$  1, DCM); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 3072, 2976, 2882, 1744, 1698, 1656;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H rotamer A}}$  1.35 (9H, s), 1.72 – 2.23 (4H, m), 3.23 – 3.55 (2H, m), 3.50 (3H, s), 4.08 – 4.17 (1H, m), 4.44 – 4.55 (2H, m), 4.78 – 4.92 (1H, m), 6.56 (1H, d,  $J = 12.6$  Hz);  $\delta_{\text{H rotamer B}}$  1.40 (9H, s), 1.72 – 2.23 (4H, m), 3.23 – 3.55 (2H, m), 3.51 (3H, s), 4.19 – 4.27 (1H, m), 4.44 – 4.55 (2H, m), 4.78 – 4.92 (1H, m), 6.58 (1H, d,  $J = 12.6$  Hz);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C rotamer A}}$  24.0, 28.7, 30.2, 46.7, 56.5, 59.3, 60.8, 80.1, 97.2, 153.7, 154.0, 173.3;  $\delta_{\text{C rotamer B}}$  24.7, 28.8, 31.2, 46.9, 56.5, 59.6, 63.4, 80.2, 97.2, 154.0, 154.2, 173.6; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{14}\text{H}_{23}\text{NO}_5\text{Na}$  308.1474, found 308.1463 ( $\text{M}+\text{Na}$ ) $^+$ .

***anti*-1-*tert*-Butyl 2-methyl 2-(1-methoxyallyl)pyrrolidine-1,2-dicarboxylate (234)**

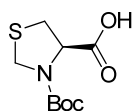
To a solution of (*S,E*)-1-*tert*-butyl 2-(3-methoxyallyl) pyrrolidine-1,2-dicarboxylate **233** (143 mg, 0.50 mmol, 1.0 eq) in THF (1.5 mL) at -78 °C was added TMSCl (186  $\mu$ l, 2.00 mmol, 2.0 eq). After 10 mins LHMDS (1M, 2.00 ml, 2.00 mmol, 2.0 eq) was added dropwise and reaction mixture allowed to warm to room temperature after a period of 30 mins, and stirred for 18 hours. The reaction was quenched by the addition of 1N HCl and brine solution (1:1, 5 mL) and extracted with DCM (3  $\times$  15 mL), EtOAc (1  $\times$  15 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to afford the crude acid. Treatment with diazomethane according to general procedure VIII and purification by flash chromatography (15:1 Pet/EtOAc + 1% NEt<sub>3</sub>) affords the methyl ester as a colourless oil. (142 mg, 95%, 2:1 rotamers). FTIR (film/cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 3001.2, 2988.4, 2875.3, 1715.2, 1698.2; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H rotamer A}}$  1.35 (9H, s), 1.30 – 1.67 (4H, m), 3.16 – 3.75 (2H, m), 3.23 (3H, s), 3.60 (3H, s), 4.28 – 4.36 (1H, m), 5.11 – 5.33 (2H, m), 5.88 – 6.06 (1H, m);  $\delta_{\text{H rotamer B}}$  1.37 (9H, s), 1.30 – 1.67 (4H, m), 3.16 – 3.75 (2H, m), 3.25 (3H, s), 3.61 (3H, s), 4.53 – 4.60 (1H, m), 5.11 – 5.33 (2H, m), 5.88 – 6.06 (1H, m); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C rotamer A}}$  23.3, 28.8, 32.4, 48.8, 52.2, 58.3, 70.2, 79.9, 82.0, 117.3, 135.6, 153.5, 173.7;  $\delta_{\text{C rotamer B}}$  23.9, 30.1, 33.9, 48.9, 52.2, 58.6, 70.8, 80.5, 82.0, 117.3, 135.6, 154.3, 173.7; HRMS (ESI, +ve) *m/z*: calcd. for C<sub>15</sub>H<sub>26</sub>NO<sub>5</sub> 300.1811, found 300.1801 (M+H)<sup>+</sup>.

***(R)*-3-(*tert*-Butoxycarbonyl)oxazolidine-4-carboxylic acid (237a)**

D-Serine (3.15 g, 30 mmol), formaldehyde (37% aq, 3.0 mL), 2N NaOH (15 mL, 30 mmol), NH<sub>2</sub>OH.HCl (200 mg, 3.0 mmol), NaOH (120 mg, 3.0 mmol), H<sub>2</sub>O (2.5 mL), acetone (17.5 mL) and Boc<sub>2</sub>O (7.20 g, 33 mmol) were combined according to general procedure VI (reaction time: 24 hours), to afford the title compound as a colourless oil

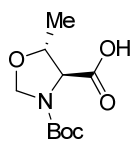
which crystallises on standing to an amorphous white solid (6.05 g, 93%).  $[\alpha]_D^{20} +70$  (*c* 1, MeOH), lit. (opp. *ent*)<sup>184</sup> -81.8 (*c* 2.6, CHCl<sub>3</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 3100, 2979, 2884, 1752, 1704, 1684; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_{\text{H rotamer A}}$  1.42 (9H, s), 4.18 (2H, bs), 4.30–4.58 (1H, m), 4.78–5.05 (2H, m), 10.75 (1H, bs);  $\delta_{\text{H rotamer B}}$  1.44 (9H, s), 4.18 (2H, bs), 4.30–4.58 (1H, m), 4.78–5.05 (2H, m), 10.75 (1H, bs); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_{\text{C rotamer A}}$  28.2, 56.8, 70.1, 79.4, 81.6, 152.3, 174.3;  $\delta_{\text{C rotamer B}}$  28.2, 57.2, 71.0, 79.4, 82.0, 153.3, 175.4; HRMS (ESI, +ve) *m/z* calcd. for C<sub>9</sub>H<sub>15</sub>NO<sub>5</sub>Na 240.0848, found: 240.0839 (M+Na)<sup>+</sup>.

**(*R*)-3-(*tert*-Butoxycarbonyl)thiazolidine-4-carboxylic acid (237b)**



L-Cysteine (30 mmol, 3.63 g), formaldehyde (37% aq, 3.0 mL), NaOH (2N, 30 mmol, 15 mL), NH<sub>2</sub>OH.HCl (200 mg, 3.0 mmol), NaOH (120 mg, 3.0 mmol), H<sub>2</sub>O (2.5 mL), acetone (17.5 mL) and Boc<sub>2</sub>O (7.20 g, 33 mmol) were combined according to general procedure VI (reaction time: 24 hours), to afford the title compound as a colourless oil which crystallises on standing to a white solid (5.41 g, 77%). Mpt: 131-133 °C (lit.<sup>288</sup> 132-133 °C);  $[\alpha]_D^{20} -117$  (*c* 1, CH<sub>2</sub>Cl<sub>2</sub>), lit.<sup>288</sup> -114 (*c* 1, MeOH); <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_{\text{H rotamer A}}$  1.45 (9H, s), 3.20–3.48 (2H, m), 4.35–4.98 (3H, m), 10.52 (1H, bs);  $\delta_{\text{H rotamer B}}$  1.49 (9H, s), 3.20–3.48 (2H, m), 4.35–4.98 (3H, m), 10.52 (1H, bs); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_{\text{C rotamer A}}$  28.3, 33.0, 48.4, 61.4, 81.8, 153.2, 175.1;  $\delta_{\text{C rotamer B}}$  29.1, 34.4, 49.0, 61.4, 81.9, 153.9, 176.3. All analytical data is in accordance with literature precedence.<sup>289</sup>

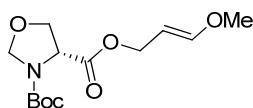
**(4*S*,5*R*)-3-(*tert*-Butoxycarbonyl)-5-methyloxazolidine-4-carboxylic acid (237c)**





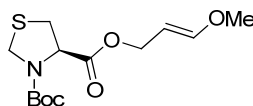
L-Threonine (3.57 g, 30 mmol), formaldehyde (37% aq, 3.0 mL), 2N NaOH (15 mL, 30 mmol),  $\text{NH}_2\text{OH}\cdot\text{HCl}$  (200 mg, 3.0 mmol), NaOH (120 mg, 3.0 mmol),  $\text{H}_2\text{O}$  (2.5 mL), acetone (17.5 mL) and  $\text{Boc}_2\text{O}$  (7.20 g, 33 mmol) were combined according to general procedure VI (reaction time: 24 hours), to afford the title compound as a colourless oil (6.76 g, 97%).  $[\alpha]_{\text{D}}^{20}$  -103 (*c* 1, MeOH), lit.<sup>184</sup> -110.2 (*c* 2,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  rotamer A: 1.37–1.63 (12H, m), 3.83–4.06 (1H, m), 4.28 (1H, bs), 4.69–4.88 (2H, m), 9.47 (1H, bs);  $\delta_{\text{H}}$  rotamer B 1.37–1.63 (12H, m), 3.83–4.06 (1H, m), 4.28 (1H, bs), 5.08–5.26 (2H, m), 9.47 (1H, bs);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  rotamer A 18.4, 28.2, 63.2, 78.3, 78.9, 81.5, 152.2, 173.8;  $\delta_{\text{C}}$  rotamer B 18.4, 28.2, 63.8, 78.8, 79.4, 82.1, 153.6, 175.5. All analytical data is in accordance with literature precedence.<sup>184</sup>

**(*R,E*)-3-*tert*-Butyl 4-(3-methoxyallyl) oxazolidine-3,4-dicarboxylate (238a)**



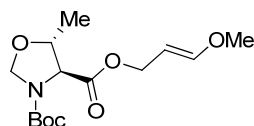
EDCI.HCl (870 mg, 4.54 mmol), triethylamine (634  $\mu\text{L}$ , 4.54 mmol), (*R*)-3-(*tert*-butoxycarbonyl)oxazolidine-4-carboxylic acid **237a** (986 mg, 4.54 mmol), DMAP (5 mol%), DCM (40 mL) and (*E*)-3-(methoxy)prop-2-enol **218a** (200 mg, 2.27 mmol) were combined according to general procedure IV (reaction time: 18 hours), to afford the title compound as a pale yellow oil (242 mg, 67%).  $[\alpha]_{\text{D}}^{20}$  +22 (*c* 1,  $\text{CH}_2\text{Cl}_2$ ); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2977, 2881, 1747, 1702, 1654;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  1.40 (9H, s), 3.51 (3H, s), 4.01 (1H, dd,  $J$  = 8.8, 4.0 Hz), 4.10–4.46 (2H, m), 4.46–4.62 (2H, m), 4.77–4.99 (3H, m), 6.60 (1H, d,  $J$  = 12.3 Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  rotamer A 27.9, 28.2, 56.1, 57.0, 63.7, 70.2, 79.5, 96.4, 152.0, 153.7, 170.5;  $\delta_{\text{C}}$  rotamer B 27.9, 28.2, 56.1, 57.5, 63.7, 71.1, 80.8, 96.4, 152.4, 153.9, 170.5; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{13}\text{H}_{21}\text{NO}_6\text{Na}$  310.1267, found: 310.1260 ( $\text{M}+\text{Na}$ )<sup>+</sup>.

**(*R,E*)-3-*tert*-Butyl 4-(3-methoxyallyl) thiazolidine-3,4-dicarboxylate (238b)**



EDCI.HCl (782 mg, 4.08 mmol), triethylamine (570  $\mu$ L, 4.08 mmol), (*R*)-3-(*tert*-butoxycarbonyl)thiazolidine-4-carboxylic acid **237b** (952 mg, 4.08 mmol), DMAP (5 mol%), DCM (40 mL) and (*E*)-3-(methoxy)prop-2-enol **218a** (180 mg, 2.04 mmol) were combined according to general procedure IV (reaction time: 18 hours), purified by flash chromatography (2:1 Pet/EtOAc + 1% NEt<sub>3</sub>) to afford the title compound as a colourless oil (389 mg, 63%).  $[\alpha]_D^{20}$  -43 (*c* 1, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2977, 2933, 1747, 1702, 1655; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_H$  rotamer A 1.36 (9H, s), 3.06–3.32 (2H, m), 3.49 (3H, s), 4.30–4.44 (1H, m), 4.45–4.91 (5H, m), 6.52–6.63 (1H, m);  $\delta_H$  rotamer B 1.41 (9H, s), 3.06–3.32 (2H, m), 3.49 (3H, s), 4.30–4.44 (1H, m), 4.45–4.91 (5H, m), 6.52–6.63 (1H, m); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_C$  rotamer A 28.2, 33.1, 48.0, 56.0, 61.6, 63.7, 81.0, 96.4, 153.0, 153.5, 170.3;  $\delta_C$  rotamer B 28.2, 34.6, 49.0, 56.0, 61.6, 63.7, 81.0, 96.4, 153.2, 153.8, 170.7; HRMS (ESI, +ve) *m/z* calcd. for C<sub>13</sub>H<sub>21</sub>NO<sub>5</sub>Na 326.1038, found: 326.1032 (M+Na)<sup>+</sup>.

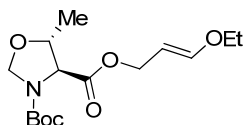
**(4*S*,5*R*)-3-*tert*-Butyl 4-((*E*)-3-methoxyallyl) 5-methyloxazolidine-3,4-dicarboxylate (238c)**



EDCI.HCl (870 mg, 4.54 mmol), triethylamine (634  $\mu$ L, 4.54 mmol), (4*S*,5*R*)-3-(*tert*-butoxycarbonyl)-5-methyloxazolidine-4-carboxylic acid **237c** (1.05 g, 4.54 mmol), DMAP (5 mol%), DCM (40 mL) and (*E*)-3-(methoxy)prop-2-enol **218a** (200 mg, 2.27 mmol) were combined according to general procedure IV (reaction time: 18 hours), purified by flash chromatography (2:1 Pet/EtOAc + 1% NEt<sub>3</sub>) to afford the title compound as a colourless oil (380 mg, 56%).  $[\alpha]_D^{20}$  -70.3 (*c* 3.2, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2978, 2937, 2873, 1748, 1705, 1653; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_H$  rotamer A 1.32 (9H, s), 1.37 (3H, bs), 3.47 (3H, s), 3.69–3.95 (1H, m), 4.05 (1H, dt, *J* = 12.6, 6.3 Hz), 4.38–4.62 (2H, m), 4.62–4.90 (2H, m), 4.91–5.15 (1H, m), 6.50–6.62 (1H, m);  $\delta_H$  rotamer B 1.34 (9H, s), 1.37 (3H, bs), 3.47 (3H, s), 3.69–3.95 (1H, m), 4.05 (1H, dt, *J* = 12.6, 6.3 Hz), 4.38–4.62 (2H, m), 4.62–4.90 (2H, m), 4.91–5.15 (1H, m), 6.50–6.62 (1H, m); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_C$  rotamer A 18.4, 28.1, 56.0, 63.5, 64.0,

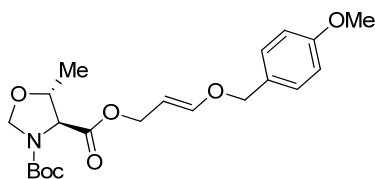
78.8, 79.2, 80.6, 96.4, 152.0, 153.6, 170.0;  $\delta_{\text{C}}$  rotamer B 18.6, 28.1, 56.0, 63.5, 64.0, 78.8, 79.2, 80.6, 96.4, 152.4, 153.9, 170.2; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{14}\text{H}_{23}\text{NO}_6\text{Na}$  324.1423, found: 324.1418 ( $\text{M}+\text{Na}$ )<sup>+</sup>.

**(4*S*,5*R*)-3-*tert*-Butyl 4-((*E*)-3-ethoxyallyl) 5-methyloxazolidine-3,4-dicarboxylate (238d)**



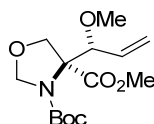
EDCI.HCl (1.15 g, 6.0 mmol), triethylamine (838  $\mu\text{L}$ , 6.0 mmol), (4*S*,5*R*)-3-(*tert*-butoxycarbonyl)-5-methyloxazolidine-4-carboxylic acid **237c** (1.39 g, 6.0 mmol), DMAP (5 mol%), DCM (250 mL) and (*E*)-3-(ethoxy)prop-2-enol **218b** (306 mg, 3.0 mmol) were combined according to general procedure IV (reaction time: 2 hours), purified by flash chromatography (2:1 Pet/EtOAc + 1%  $\text{NEt}_3$ ) to afford the title compound as a colourless oil (427 mg, 45%).  $[\alpha]_{\text{D}}^{20}$  -67.6 ( $c$  2.9,  $\text{CHCl}_3$ ); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2979, 2936, 2880, 1749, 1703, 1653;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  rotamer A 1.27 (3H, t,  $J$  = 7.0 Hz), 1.40 (3H, d,  $J$  = 6.2 Hz), 1.42 (9H, s), 3.81 (2H, q,  $J$  = 7.0 Hz), 3.83–3.92 (1H, m), 4.08–4.25 (1H, m), 4.49–4.58 (1H, m), 4.60 (1H, app. d,  $J$  = 7.7 Hz), 4.73 (1H, d,  $J$  = 4.0 Hz), 4.91–5.03 (1H, m), 5.06 (1H, d,  $J$  = 4.0 Hz), 6.72 (1H, m);  $\delta_{\text{H}}$  rotamer B 1.27 (3H, t,  $J$  = 7.0 Hz), 1.40 (3H, d,  $J$  = 6.2 Hz), 1.47 (9H, s), 3.81 (2H, q,  $J$  = 7.0 Hz), 3.83–3.92 (1H, m), 4.08–4.25 (1H, m), 4.49–4.58 (1H, m), 4.60 (1H, app. d,  $J$  = 7.7 Hz), 4.73 (1H, d,  $J$  = 4.0 Hz), 4.91–5.03 (1H, m), 5.06 (1H, d,  $J$  = 4.0 Hz), 6.72 (1H, m);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  rotamer A 13.9, 17.9, 27.6, 63.3, 63.5, 64.8, 78.4, 79.3, 79.9, 95.9, 151.7, 152.8, 169.7;  $\delta_{\text{C}}$  rotamer B 14.1, 18.1, 27.6, 63.3, 64.0, 66.8, 78.6, 79.3, 80.0, 97.4, 152.1, 153.1, 170.0; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{15}\text{H}_{25}\text{NO}_6\text{Na}$  338.1580, found: 338.1601 ( $\text{M}+\text{Na}$ )<sup>+</sup>.

**(4*S*,5*R*)-3-*tert*-Butyl 4-((*E*)-3-(4-methoxybenzyloxy)allyl) 5-methyloxazolidine-3,4-dicarboxylate (238e)**



EDCI.HCl (2.30 g, 12.0 mmol), triethylamine (1.68 mL, 12.0 mmol), (4*S*,5*R*)-3-(*tert*-butoxycarbonyl)-5-methyloxazolidine-4-carboxylic acid **237c** (2.78 g, 12.0 mmol), DMAP (5 mol%), DCM (250 mL) and (*E*)-3-(4-methoxybenzyloxy)prop-2-en-1-ol **218k** (1.17 g, 6.0 mmol) were combined according to general procedure IV (reaction time: 2 hours) to afford the title compound as a yellow oil (1.55 g, 64%).  $[\alpha]_D^{20}$  -55.2 (c 1.45, CHCl<sub>3</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2978, 2936, 2878, 1748, 1704, 1672, 1651; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_H$  mixture of rotamers 1.36–1.50 (12H, m), 3.78 (3H, s), 3.79–4.03 (1H, m), 4.07–4.15 (1H, m), 4.46–4.67 (2H, m), 4.68 (2H, s), 4.73–4.85 (1H, m), 4.95–5.24 (2H, m), 6.66 (1H, app. d,  $J$  = 12.0 Hz), 6.87 (2H, app. d,  $J$  = 8.5 Hz), 7.24 (2H, app. d,  $J$  = 8.5 Hz); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_C$  rotamer A 18.5, 28.1, 55.2, 63.5, 64.1, 66.9, 71.3, 78.5, 78.9, 79.3, 80.8, 98.1, 114.0, 129.3, 152.5, 159.6, 170.1;  $\delta_C$  rotamer B 18.6, 28.2, 55.2, 63.6, 64.1, 66.9, 71.3, 78.5, 78.9, 79.3, 80.8, 98.1, 114.0, 129.3, 152.8, 159.6, 170.2; HRMS (ESI, +ve)  $m/z$  calcd. for C<sub>21</sub>H<sub>29</sub>NO<sub>7</sub>Na 430.1842, found: 430.1852 (M+Na)<sup>+</sup>.

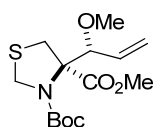
**(±)-(*anti*)-3-*tert*-Butyl 4-methyl 4-(1-methoxyallyl)oxazolidine-3,4-dicarboxylate (239a)**



To a solution of (*R,E*)-3-*tert*-butyl 4-(3-methoxyallyl) oxazolidine-3,4-dicarboxylate **238a** (50 mg, 0.174 mmol) in THF (0.5 mL) at -78 °C was added TMSCl (67  $\mu$ L, 0.522 mmol). After 10 mins LHMDS (1M, 522  $\mu$ L, 0.522 mmol) was added *via* syringe pump at an addition rate of 3 mL min<sup>-1</sup> and reaction mixture allowed to warm to room

temperature after a period of 30 mins, and stirred for 18 hours. The reaction was quenched by the addition of 1N HCl and brine solution (1:1, 5 mL) and extracted with DCM (3 × 15 mL), EtOAc (1 × 15 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to afford the crude acid. Treatment with diazomethane according to general procedure VIII and purification by flash chromatography (8:1 Pet/EtOAc + 1% NEt<sub>3</sub>) affords the methyl ester as a colourless oil (26 mg, 50%, dr 6:1). FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2981, 2934, 1743, 1698; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  major diastereomer 1.47 (9H, s), 3.37 (3H, s), 3.75 (3H, s), 4.70–4.88 (2H, m), 4.28–4.65 (1H, m), 4.70–4.88 (1H, m), 5.07–5.44 (3H, m), 5.90–6.08 (1H, m);  $\delta_{\text{H}}$  minor diastereomer 1.44 (9H, s), 3.35 (3H, s), 3.78 (3H, s), 4.70–4.88 (2H, m), 4.28–4.65 (1H, m), 4.70–4.88 (1H, m), 5.07–5.44 (3H, m), 5.68–5.78 (1H, m); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  major diastereomer 28.3, 52.4, 57.7, 67.7, 72.1, 73.4, 80.7, 81.3, 118.4, 133.7, 151.4, 171.0;  $\delta_{\text{C}}$  minor diastereomer 28.2, 52.5, 58.0, 68.3, 72.3, 73.1, 80.3, 81.0, 118.4, 133.7, 151.8, 171.7; HRMS (ESI, +ve) *m/z* calcd. for C<sub>14</sub>H<sub>23</sub>NO<sub>6</sub>Na 324.1423, found: 324.1422 (M+Na)<sup>+</sup>.

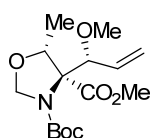
**(±)-(anti)-3-*tert*-Butyl 4-methyl 4-(1-methoxyallyl)thiazolidine-3,4-dicarboxylate (239b)**



To a solution of (*R,E*)-3-*tert*-butyl 4-(3-methoxyallyl) thiazolidine-3,4-dicarboxylate **238b** (75 mg, 0.247 mmol) in THF (0.75 mL) at -78 °C was added TMSCl (95  $\mu$ L, 0.742 mmol). After 10 mins LHMDS (1M, 742  $\mu$ L, 0.742 mmol) was added *via* syringe pump at an addition rate of 3 mL min<sup>-1</sup> and reaction mixture allowed to warm to room temperature after a period of 30 mins, and stirred for 18 hours. The reaction was quenched by the addition of 1N HCl and brine solution (1:1, 5 mL) and extracted with DCM (3 × 15 mL), EtOAc (1 × 15 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to afford the crude acid. Treatment with diazomethane according to general procedure VIII and purification by flash chromatography (8:1 Pet/EtOAc + 1% NEt<sub>3</sub>) affords the methyl ester as a colourless oil (34.4 mg, 44%, dr 12:1). FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2979, 2932, 2830, 1741, 1694; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  major diastereomer 1.47 (9H, s), 3.03

(1H, d,  $J = 12.4$  Hz), 3.33 (3H, s), 3.40–3.58 (1H, m), 3.73 (3H, s), 4.39 (0.5H, bs), 4.42 (1H, d,  $J = 9.1$  Hz), 4.64 (0.5H, bs), 4.75 (0.5H, bs), 4.91 (0.5H, bs), 5.31 (1H, app. d,  $J = 9.5$  Hz), 5.38 (1H, app. d,  $J = 16.8$  Hz), 6.13 (1H, ddd,  $J = 16.8, 9.5, 6.1$  Hz);  $\delta_{\text{H}}$  minor diastereomer 1.44 (9H, s), 3.03 (1H, d,  $J = 12.4$  Hz), 3.38 (3H, s), 3.40–3.58 (1H, m), 3.77 (3H, s), 4.39 (0.5H, bs), 4.42 (1H, d,  $J = 9.1$  Hz), 4.64 (0.5H, bs), 4.75 (0.5H, bs), 4.91 (0.5H, bs), 5.31 (1H, app. d,  $J = 9.5$  Hz), 5.38 (1H, app. d,  $J = 16.8$  Hz), 5.83 (1H, ddd,  $J = 16.8, 9.5, 6.1$  Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  major diastereomer 28.2, 36.5, 51.2, 52.4, 57.8, 72.9, 80.6, 81.8, 118.1, 134.4, 152.3, 171.3; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{14}\text{H}_{23}\text{NO}_5\text{SNa}$  340.1195, found: 340.1188 ( $\text{M}+\text{Na}$ ) $^+$ .

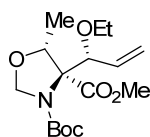
**(4*S*,5*R*)-3-*tert*-Butyl 4-methyl 4-((*R*)-1-methoxyallyl)-5-methyloxazolidine-3,4-dicarboxylate (239c)**



To a solution of (4*S*,5*R*)-3-*tert*-butyl 4-((*E*)-3-methoxyallyl) 5-methyloxazolidine-3,4-dicarboxylate **238c** (150 mg, 0.500 mmol) in THF (1.5 mL) at  $-78$  °C was added TMSCl (191  $\mu\text{L}$ , 1.50 mmol). After 10 mins LHMDs (1M, 1.50 mL, 1.50 mmol) was added *via* syringe pump at an addition rate of  $3\text{ mL min}^{-1}$  and reaction mixture allowed to warm to room temperature after a period of 30 mins, and stirred for 18 hours. The reaction was quenched by the addition of 1N HCl and brine solution (1:1, 5 mL) and extracted with DCM ( $3 \times 15\text{ mL}$ ), EtOAc ( $1 \times 15\text{ mL}$ ), dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo* to afford the crude acid. Treatment with diazomethane according to general procedure VIII and purification by flash chromatography (10:1 Pet/EtOAc) affords the methyl ester as a colourless oil (74 mg, 47%, dr >99:1).  $[\alpha]_{\text{D}}^{20} -54.0$  ( $c$  1,  $\text{CH}_2\text{Cl}_2$ ); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2981, 2942, 2871, 1742, 1705;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ , 328K)  $\delta_{\text{H}}$  rotamer A 1.18 (3H, d,  $J = 3.9$  Hz), 1.46 (9H, s), 3.36 (3H, s), 3.74 (3H, s), 4.20–4.28 (1H, m), 4.39 (1H, app. d,  $J = 4.3$  Hz), 4.67 (1H, d,  $J = 4.0$  Hz), 5.16 (1H, d,  $J = 4.0$  Hz), 5.26–5.35 (1H, m), 5.41 (1H, dd,  $J = 17.4, 1.7$  Hz), 6.10–6.20 (1H, m);  $\delta_{\text{H}}$  rotamer B 1.20 (3H, d,  $J = 3.9$  Hz), 1.48 (9H, s), 3.38 (3H, s), 3.75 (3H, s), 4.20–4.28 (1H, m), 4.62 (1H, app. d,  $J = 4.3$  Hz), 4.70 (1H, d,  $J = 4.0$  Hz), 5.26–5.35 (2H, m), 5.41

(1H, dd,  $J = 17.4, 1.7$  Hz), 6.10–6.20 (1H, m);  $^{13}\text{C}$  NMR (75MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  rotamer A 15.3, 27.3, 50.8, 57.1, 76.2, 77.7, 78.4, 79.6, 115.9, 127.2, 133.1, 150.3, 169.5;  $\delta_{\text{C}}$  rotamer B 15.4, 27.3, 50.9, 57.3, 76.8, 77.9, 78.5, 79.9, 116.2, 128.0, 133.2, 150.8, 169.6; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{15}\text{H}_{25}\text{NO}_6\text{Na}$  338.1580, found: 338.1551 ( $\text{M}+\text{Na}$ ) $^{+}$ .

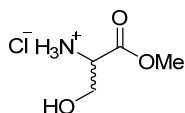
**(4*S*,5*R*)-3-*tert*-Butyl 4-methyl 4-((*R*)-1-ethoxyallyl)-5-methyloxazolidine-3,4-dicarboxylate (239d)**



To a solution of (4*S*,5*R*)-3-*tert*-butyl 4-((*E*)-3-ethoxyallyl) 5-methyloxazolidine-3,4-dicarboxylate **238d** (191 mg, 0.61 mmol) in THF (4.0 mL) at  $-78^{\circ}\text{C}$  was added  $\text{TMSCl}$  (232  $\mu\text{L}$ , 1.82 mmol). After 10 mins LHMDS (1M, 1.82 mL, 1.82 mmol) was added *via* syringe pump at an addition rate of  $3\text{ mL min}^{-1}$  and reaction mixture allowed to warm to room temperature after a period of 30 mins, and stirred for 18 hours. The reaction was quenched by the addition of 1N HCl and brine solution (1:1, 5 mL) and extracted with DCM ( $3 \times 15\text{ mL}$ ), EtOAc ( $1 \times 15\text{ mL}$ ), dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo* to afford the crude acid. Treatment with diazomethane according to general procedure VIII and purification by flash chromatography (10:1 Pet/EtOAc) affords the methyl ester as a colourless oil (140 mg, 70%, dr >99:1).  $[\alpha]_{\text{D}}^{20} -62.7$  ( $c$  1.9,  $\text{CHCl}_3$ ); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2977, 2874, 1742, 1704;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ , 328K)  $\delta_{\text{H}}$  rotamer A 1.08–1.15 (6H, m), 1.39 (9H, s), 3.33–3.43 (1H, m), 3.51–3.61 (1H, m), 3.68 (3H, s), 4.21 (1H, app. sex,  $J = 6.0$  Hz), 4.42–4.48 (1H, m), 4.61 (1H, d,  $J = 3.9$  Hz), 5.11 (1H, d,  $J = 3.9$  Hz), 5.20 (1H, app. t,  $J = 10.8$  Hz), 5.37 (1H, app. dd,  $J = 17.2, 2.3$  Hz), 6.11–6.21 (1H, m);  $\delta_{\text{H}}$  rotamer B 1.08–1.15 (6H, m), 1.41 (9H, s), 3.33–3.43 (1H, m), 3.51–3.61 (1H, m), 3.69 (3H, s), 4.21 (1H, app. sex,  $J = 6.0$  Hz), 4.64 (1H, d,  $J = 3.9$  Hz), 4.66–4.70 (1H, m), 5.20 (1H, app. t,  $J = 10.8$  Hz), 5.28 (1H, d,  $J = 3.9$  Hz), 5.37 (1H, app. dd,  $J = 17.2, 2.3$  Hz), 6.11–6.21 (1H, m);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  rotamer A 15.4, 16.3, 28.3, 51.8, 65.8, 70.8, 77.7, 78.8, 79.4, 80.5, 116.5, 134.8, 151.2, 170.5;  $\delta_{\text{C}}$  rotamer B 15.4, 16.4, 28.3, 51.9, 66.2, 70.8, 78.0, 78.8, 79.6, 80.8, 116.7, 135.0,

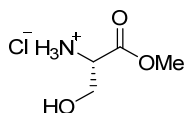
151.7, 170.7; HRMS (ESI, +ve)  $m/z$  calcd. for  $C_{16}H_{27}NO_6Na$  352.1736, found: 352.1716 ( $M+Na$ )<sup>+</sup>.

**DL-Serine methyl ester hydrochloride (*rac*-247)**



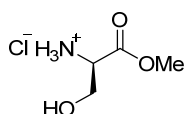
DL-Serine (20.2 g, 193 mmol) in MeOH (400 mL) and thionyl chloride (28.0 mL, 385 mmol, 2.0 eq) were combined according to general procedure V to afford DL-serine methyl ester hydrochloride as a white powder (29.6 g, 99%). Mpt: 138-141 °C (lit.<sup>290</sup> 135-136 °C); <sup>1</sup>H NMR (500MHz, D<sub>2</sub>O)  $\delta_H$  3.81 (3H, s), 3.95 (1H, dd,  $J$  = 4.0, 12.5 Hz), 4.05 (1H, dd,  $J$  = 4.0, 12.5 Hz), 4.24 (1H, app. t,  $J$  = 4.0 Hz), 4.69 (3H, s); <sup>13</sup>C NMR (125MHz, D<sub>2</sub>O)  $\delta_C$  53.7, 54.7, 59.2, 168.9. All analytical data is in accordance with literature precedence.<sup>291</sup>

**L-Serine methyl ester hydrochloride hydrochloride (247)**



L-Serine (20.2 g, 193 mmol) in MeOH (400 mL) and thionyl chloride (28.0 mL, 385 mmol, 2.0 eq) were combined according to general procedure V to afford L-serine methyl ester hydrochloride as a white powder (29.8 g, 99%). Mpt: 162-163 °C (lit.<sup>292</sup> 162-165 °C);  $[\alpha]_D^{20}$  +5 ( $c$  1, MeOH), lit.<sup>293</sup>  $[\alpha]_D^{20}$  +5 ( $c$  2, MeOH). All other data as previously stated.

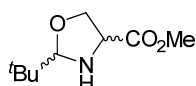
**D-Serine methyl ester hydrochloride hydrochloride (*ent*-247)**





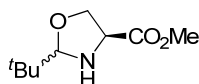
D-Serine (10.1 g, 96.5 mmol) in MeOH (200 mL) and thionyl chloride (14.0 mL, 193 mmol, 2.0 eq) were combined according to general procedure V to afford D-serine methyl ester hydrochloride as a white powder (14.8 g, 99%). Mpt: 162-165 °C (lit.<sup>294</sup> 163-164 °C);  $[\alpha]_{\text{D}}^{20}$  -5 (c 1, MeOH), lit.<sup>295</sup>  $[\alpha]_{\text{D}}^{20}$  -5.2 (c 0.4, MeOH). All other data as previously stated.

**(±)-Methyl 2-*tert*-butyloxazolidine-4-carboxylate (*rac*-248)**



To a suspension of DL-serine methyl ester hydrochloride *rac*-**247** (7.02 g, 45.1 mmol, 1.0 eq) in pentane (125 mL) was added pivalaldehyde (7.35 mL, 67.7 mmol, 1.5 eq) and triethylamine (6.93 mL, 49.6 mmol, 1.1 eq) and the reaction refluxed at 55 °C for 72 hours under Dean Stark conditions. The resulting mixture was allowed to cool to room temperature, filtered, and the solid washed with pentane. The combined filtrate was concentrated *in vacuo* to afford the title compound as a pale yellow liquid (7.50 g, 89%, dr 60:40). FTIR (film/cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 3320, 2957, 2909, 2872, 1740; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  major diastereomer 1.00 (9H, s), 2.95 (1H, bs), 3.69–3.79 (1H, m), 3.77 (3H, s), 3.89–4.15 (2H, m), 4.09 (1H, s);  $\delta_{\text{H}}$  minor diastereomer 0.92 (9H, s), 2.95 (1H, bs), 3.69–3.79 (1H, m), 3.75 (3H, s), 3.89–4.15 (2H, m), 4.34 (1H, s); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  major diastereomer 25.2, 33.2, 52.5, 59.5, 68.3, 99.9, 172.8;  $\delta_{\text{C}}$  minor diastereomer 24.9, 34.5, 52.3, 59.4, 68.9, 99.2, 173.1; HRMS (ESI, +ve) *m/z* calcd. for C<sub>9</sub>H<sub>17</sub>NO<sub>3</sub>Na 210.1106, found: 210.1096 (M+Na)<sup>+</sup>.

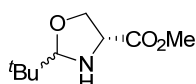
**(*S*)-Methyl 2-*tert*-butyloxazolidine-4-carboxylate (**248**)**



To a suspension of L-serine methyl ester hydrochloride **247** (6.0 g, 38.6 mmol, 1.0 eq) in pentane (150 mL) was added pivalaldehyde (6.30 mL, 57.9 mmol, 1.5 eq) and triethylamine (6.0 mL, 42.5 mmol, 1.1 eq) and the reaction refluxed at 55 °C for 72

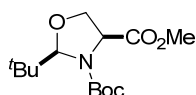
hours under Dean Stark conditions. The resulting mixture was allowed to cool to room temperature, filtered, and the solid washed with pentane. The combined filtrate was concentrated *in vacuo* to afford the title compound as a pale yellow liquid (6.84 g, 95%, dr 63:37). All other data as previously stated, and in accordance with literature precedence.<sup>296</sup>

**(*R*)-Methyl 2-*tert*-butyloxazolidine-4-carboxylate (*ent*-248)**



To a suspension of D-serine methyl ester hydrochloride *ent*-247 (7.78 g, 50.0 mmol, 1.0 eq) in pentane (150 mL) was added pivalaldehyde (8.14 mL, 75.0 mmol, 1.5 eq) and triethylamine (7.68 mL, 55.0 mmol, 1.1 eq) and the reaction refluxed at 55 °C for 72 hours under Dean Stark conditions. The resulting mixture was allowed to cool to room temperature, filtered, and the solid washed with pentane. The combined filtrate was concentrated *in vacuo* to afford the title compound as a pale yellow liquid (8.76 g, 94%, dr 60:40). All other data as previously stated, and in accordance with literature precedence.<sup>201</sup>

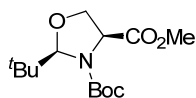
**(±)-(*syn*)-3-*tert*-Butyl 4-methyl 2-*tert*-butyloxazolidine-3,4-dicarboxylate (*rac*-249)**



To a solution of (±)-methyl 2-*tert*-butyloxazolidine-4-carboxylate *rac*-248 (4.63 g, 24.7 mmol, 1.0 eq) and NaHCO<sub>3</sub> (5.19 g, 61.8 mmol, 2.5 eq) in MeOH (80 mL) was added Boc<sub>2</sub>O (5.37 g, 24.7 mmol, 1.0 eq) and allowed to stir vigorously at 50 °C for 18 hours. The resulting mixture was allowed to cool to room temperature, filtered and the filtrate concentrated *in vacuo*. The residue was diluted with diethyl ether, washed with brine (1 × 75 mL), dried over MgSO<sub>4</sub> and concentrated *in vacuo*. Purification by flash chromatography 4:1 Pet/EtOAc afforded the title compound as a colourless liquid (4.67 g, 66%, dr >99:1). FTIR (film/cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 2975, 2908, 1762, 1741, 1704; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  0.92 (9H, s), 1.46 (9H, s), 3.74 (3H, s), 4.10 (1H, app. t, *J* = 7.2

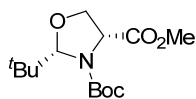
Hz), 4.26 (1H, app. t,  $J = 7.2$  Hz), 4.68 (1H, bs), 5.01 (1H, s);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  25.7, 28.2, 37.7, 52.2, 59.7, 68.3, 81.3, 97.6, 155.1, 171.0; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{14}\text{H}_{25}\text{NO}_5\text{Na}$  310.1630, found: 310.1626 ( $\text{M}+\text{Na}$ ) $^{+}$ .

**(2R,4S)-3-*tert*-Butyl 4-methyl 2-*tert*-butyloxazolidine-3,4-dicarboxylate (249)**



To a solution of (*S*)-methyl 2-*tert*-butyloxazolidine-4-carboxylate **248** (a 60:40 mixture of diastereomers) (2.46 g, 13.1 mmol, 1.0 eq) and  $\text{NaHCO}_3$  (2.75 g, 32.8 mmol, 2.5 eq) in MeOH (40 mL) was added  $\text{Boc}_2\text{O}$  (2.85 g, 13.1 mmol, 1.0 eq) and allowed to stir vigorously at 50 °C for 18 hours. The resulting mixture was allowed to cool to room temperature, filtered and the filtrate concentrated *in vacuo*. The residue was diluted with diethyl ether, washed with brine (1  $\times$  50 mL), dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to afford the crude compound with a dr >98:2. Purification by flash chromatography (4:1 Pet/EtOAc) afforded the title compound as a colourless liquid (2.62 g, 70%, dr >99:1).  $[\alpha]_{\text{D}}^{20}$  -30 ( $c$  2,  $\text{CH}_2\text{Cl}_2$ ), lit.<sup>196</sup>  $[\alpha]_{\text{D}}^{20}$  -30 ( $c$  0.3, MeOH). All other data as previously stated, and in accordance with literature precedence.<sup>196</sup>

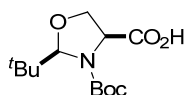
**(2S,4R)-3-*tert*-Butyl 4-methyl 2-*tert*-butyloxazolidine-3,4-dicarboxylate (*ent*-249)**



To a solution of (*R*)-Methyl 2-*tert*-butyloxazolidine-4-carboxylate *ent*-**248** (a 60:40 mixture of diastereomers) (6.00 g, 32.0 mmol, 1.0 eq) and  $\text{NaHCO}_3$  (6.72 g, 80.0 mmol, 2.5 eq) in MeOH (125 mL) was added  $\text{Boc}_2\text{O}$  (6.95 g, 32.0 mmol, 1.0 eq) and allowed to stir vigorously at 50 °C for 18 hours. The resulting mixture was allowed to cool to room temperature, filtered and the filtrate concentrated *in vacuo*. The residue was diluted with diethyl ether, washed with brine (1  $\times$  75 mL), dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to afford the crude compound with a dr >98:2. Purification by flash chromatography (4:1 Pet/EtOAc) afforded the title compound as a colourless

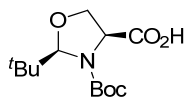
liquid (6.41 g, 70%, dr >99:1).  $[\alpha]_D^{20} +29$  ( $c$  2.4,  $\text{CH}_2\text{Cl}_2$ ). All other data as previously stated.

**(±)-(syn)-3-(tert-Butoxycarbonyl)-2-tert-butyloxazolidine-4-carboxylic acid (*rac*-250)**



To a solution of (±)-(syn)-3-*tert*-butyl 4-methyl 2-*tert*-butyloxazolidine-3,4-dicarboxylate *rac*-**249** (4.16 g, 14.5 mmol, 1.0 eq) in MeOH (29 mL) at 0 °C was added 3N KOH (9.65 mL, 29.0 mmol, 2.0 eq) dropwise and the reaction mixture allowed to stir at room temperature for 4 hours. The solvent was removed *in vacuo* and the residue diluted with ether, then acidified with 3N HCl till pH 1-2 and then extracted with ether. The combined organics were washed with brine (1 × 50 mL), dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to afford the title compound as a white solid (3.55 g, 90%, dr >99:1). FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 3191, 2981, 2890, 1703;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  0.92 (9H, s), 1.50 (9H, s), 4.22 (1H, t,  $J = 8.8$  Hz), 4.44 (1H, dd,  $J = 8.8, 6.5$  Hz), 4.65 (1H, dd,  $J = 8.8, 6.5$  Hz), 5.06 (1H, s), 9.70 (1H, bs);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  25.6, 28.0, 37.7, 59.3, 67.7, 83.1, 97.3, 156.7, 172.6; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{13}\text{H}_{23}\text{NO}_5\text{Na}$  296.1474, found: 296.1468 ( $\text{M}+\text{Na}$ ) $^+$ .

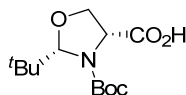
**(2*R*,4*S*)-3-(tert-Butoxycarbonyl)-2-tert-butyloxazolidine-4-carboxylic acid (250)**



To a solution of (2*R*,4*S*)-3-*tert*-butyl 4-methyl 2-*tert*-butyloxazolidine-3,4-dicarboxylate **249** (5.54 g, 19.3 mmol, 1.0 eq) in MeOH (20 mL) at 0 °C was added 3N KOH (12.9 mL, 38.6 mmol, 2.0 eq) dropwise and the reaction mixture allowed to stir at room temperature for 4 hours. The solvent was removed *in vacuo* and the residue diluted with ether, then acidified with 3N HCl till pH 1-2 and then extracted with ether. The combined organics were washed with brine (1 × 50 mL), dried over  $\text{MgSO}_4$  and

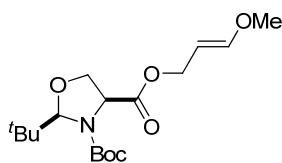
concentrated *in vacuo* to afford the title compound as a white solid (4.68 g, 89%, dr >99:1). Mpt: 134-136 °C (lit.<sup>191</sup> 106-109 °C);  $[\alpha]_D^{20}$  -98 (*c* 3.5, CH<sub>2</sub>Cl<sub>2</sub>), lit.<sup>191</sup>  $[\alpha]_D^{20}$  -64 (*c* 1, CHCl<sub>3</sub>). All other data as previously stated, and in accordance with literature precedence.<sup>191</sup>

**(2*S*,4*R*)-3-(*tert*-Butoxycarbonyl)-2-*tert*-butyloxazolidine-4-carboxylic acid (*ent*-250)**



To a solution of (2*S*,4*R*)-3-*tert*-butyl 4-methyl 2-*tert*-butyloxazolidine-3,4-dicarboxylate *ent*-249 (5.76 g, 20.0 mmol, 1.0 eq) in MeOH (20 mL) at 0 °C was added 3N KOH (14 mL, 40.0 mmol, 2.0 eq) dropwise and the reaction mixture allowed to stir at room temperature for 4 hours. The solvent was removed *in vacuo* and the residue diluted with ether, then acidified with 3N HCl till pH 1-2 and then extracted with ether. The combined organics were washed with brine (1 × 50 mL), dried over MgSO<sub>4</sub> and concentrated *in vacuo* to afford the title compound as a white solid (4.97 g, 91%, dr >99:1). Mpt: 134-135 °C (lit.<sup>191</sup> 103-105 °C);  $[\alpha]_D^{20}$  +99 (*c* 3, CH<sub>2</sub>Cl<sub>2</sub>). All other data as previously stated.

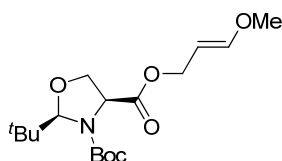
**(±)-(syn)-3-*tert*-Butyl 4-((*E*)-3-methoxyallyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate (*rac*-251a)**



EDCI.HCl (2.49 g, 13.0 mmol), triethylamine (1.82 mL, 13.0 mmol), (±)-(syn)-3-(*tert*-butoxycarbonyl)-2-*tert*-butyloxazolidine-4-carboxylic acid *rac*-250 (3.54 g, 13.0 mmol), DMAP (5 mol%), DCM (125 mL) and (*E*)-3-(methoxy)prop-2-enol **218a** (9.19 mmol, 810 mg) were combined according to general procedure IV (reaction time: 2 hours) to afford the title compound as a yellow oil without the need for further purification (3.12 g, 99%). FTIR (film/cm-1)  $\nu_{\text{max}}$ : 2961, 2907, 1755, 1705, 1654; <sup>1</sup>H

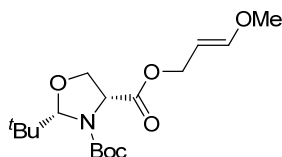
NMR (500MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  0.93 (9H, s), 1.46 (9H, s), 3.54 (3H, s), 4.15 (1H, app. t,  $J$  = 8.4 Hz), 4.23 (1H, dd,  $J$  = 8.4, 6.0 Hz), 4.57 (2H, dd,  $J$  = 7.8, 3.8 Hz), 4.64 (1H, bs), 4.91 (1H, dt,  $J$  = 12.7, 7.8 Hz), 5.02 (1H, s), 6.64 (1H, d,  $J$  = 12.7 Hz); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  25.8, 28.2, 37.8, 56.0, 59.8, 63.5, 68.4, 81.2, 96.5, 97.6, 153.7, 155.0, 170.4; HRMS (ESI, +ve)  $m/z$  calcd. for C<sub>17</sub>H<sub>29</sub>NO<sub>6</sub>Na 366.1893, found: 366.1895 (M+Na)<sup>+</sup>.

**(2*R*,4*S*)-3-*tert*-Butyl 4-((*E*)-3-methoxyallyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate (251a)**



EDCI.HCl (456 mg, 2.38 mmol), triethylamine (335  $\mu$ L, 2.38 mmol), (2*R*,4*S*)-3-(*tert*-butoxycarbonyl)-2-*tert*-butyloxazolidine-4-carboxylic acid **250** (650 mg, 2.38 mmol), DMAP (5 mol%), DCM (40 mL) and (*E*)-3-(methoxy)prop-2-enol **218a** (140 mg, 1.59 mmol) were combined according to general procedure IV (reaction time: 2 hours). Purified on a short pad of silica (2:1 Pet:EtOAc + 1% NEt<sub>3</sub>) to afford the title compound as a colourless oil (495 mg, 91%).  $[\alpha]_{\text{D}}^{20}$  -22.5 ( $c$  2, CH<sub>2</sub>Cl<sub>2</sub>). All other data as previously stated.

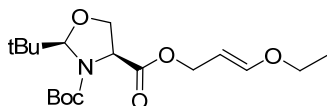
**(2*S*,4*R*)-3-*tert*-Butyl 4-((*E*)-3-methoxyallyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate (*ent*-251a)**



EDCI.HCl (383 mg, 2.00 mmol), triethylamine (280  $\mu$ L, 2.00 mmol), (2*S*,4*R*)-3-(*tert*-butoxycarbonyl)-2-*tert*-butyloxazolidine-4-carboxylic acid *ent*-**250** (546 mg, 2.38 mmol), DMAP (5 mol%), DCM (50 mL) and (*E*)-3-(methoxy)prop-2-enol **218a** (88 mg, 1.59 mmol) were combined according to general procedure IV (reaction time: 2 hours).

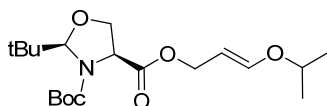
Purified on a short pad of silica (2:1 Pet:EtOAc + 1% NEt<sub>3</sub>) to afford the title compound as a colourless oil (299 mg, 87%).  $[\alpha]_{\text{D}}^{20} +22.5$  (*c* 2, CH<sub>2</sub>Cl<sub>2</sub>). All other data as previously stated.

**(2*R*,4*S*)-3-*tert*-Butyl 4-((*E*)-3-ethoxyallyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate (251b)**



EDCi.HCl (383 mg, 2.00 mmol), triethylamine (280  $\mu$ L, 2.00 mmol), (2*R*,4*S*)-3-(*tert*-butoxycarbonyl)-2-*tert*-butyloxazolidine-4-carboxylic acid **250** (547 mg, 2.00 mmol), DMAP (5 mol%), DCM (50 mL) and (*E*)-3-(ethoxy)prop-2-enol **218b** (102 mg, 1.00 mmol) were combined according to general procedure IV (reaction time: 1 hour) to afford the title compound as a yellow oil without the need for further purification (331 mg, 93%).  $[\alpha]_{\text{D}}^{20} -26$  (*c* 1, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 2976, 2939, 2875, 1755, 1705, 1673, 1653; <sup>1</sup>H NMR (500MHz, d<sub>6</sub>-acetone)  $\delta_{\text{H}}$  0.93 (9H, s), 1.25 (3H, d, *J* = 7.0 Hz), 1.46 (9H, s), 3.79 (2H, q, *J* = 7.0 Hz), 4.13–4.22 (2H, m), 4.57 (2H, d, *J* = 7.8 Hz), 4.70 (1H, dd, *J* = 7.9, 6.2 Hz), 4.92–5.04 (2H, m), 6.70 (1H, d, *J* = 12.6 Hz); <sup>13</sup>C NMR (125MHz, d<sub>6</sub>-acetone)  $\delta_{\text{C}}$  14.0, 25.4, 27.5, 37.5, 59.8, 63.1, 64.7, 68.2, 80.3, 97.2, 97.4, 152.8, 154.8, 170.1; HRMS (ESI, +ve) *m/z* calcd. for C<sub>18</sub>H<sub>31</sub>NO<sub>6</sub>Na 380.2049, found: 380.2040 (M+Na)<sup>+</sup>.

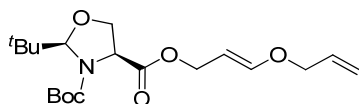
**(2*R*,4*S*)-3-*tert*-Butyl 4-((*E*)-3-isopropoxyallyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate**



EDCi.HCl (383 mg, 2.00 mmol), triethylamine (280  $\mu$ L, 2.00 mmol), (2*R*,4*S*)-3-(*tert*-butoxycarbonyl)-2-*tert*-butyloxazolidine-4-carboxylic acid **250** (547 mg, 2.00 mmol), DMAP (5 mol%), DCM (50 mL) and (*E*)-3-(isopropoxy)prop-2-enol **218c** (116 mg, 1.00 mmol) were combined according to general procedure IV (reaction time: 20

minutes), purified by flash chromatography (4:1 Pet:EtOAc, Brockmann Grade I Basic Alumina) to afford the title compound as a colourless oil (133 mg, 36%).  $[\alpha]_D^{20}$  -19 (*c* 1, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2978, 2936, 2875, 1751, 1702, 1671, 1652; <sup>1</sup>H NMR (500MHz, d<sub>6</sub>-acetone)  $\delta_H$  0.93 (9H, s), 1.21 (6H, d, *J* = 6.2 Hz), 1.46 (9H, s), 4.08–4.21 (3H, m), 4.56 (2H, d, *J* = 8.1 Hz), 4.70 (1H, app. t, *J* = 7.8 Hz), 4.94–5.03 (2H, m), 6.62 (1H, d, *J* = 12.5 Hz); <sup>13</sup>C NMR (125MHz, d<sub>6</sub>-acetone)  $\delta_C$  21.4, 25.4, 27.5, 37.5, 59.8, 63.2, 68.2, 72.8, 80.2, 97.2, 98.6, 152.0, 154.8, 170.1; HRMS (ESI, +ve) *m/z* calcd. for C<sub>19</sub>H<sub>33</sub>NO<sub>6</sub>Na 394.2206, found: 394.2209 (M+Na)<sup>+</sup>.

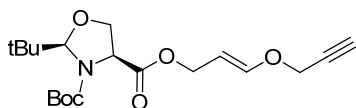
**(2*R*,4*S*)-4-((*E*)-3-(Allyloxy)allyl) 3-*tert*-butyl 2-*tert*-butyloxazolidine-3,4-dicarboxylate (251d)**



EDCi.HCl (767 mg, 4.00 mmol), triethylamine (560  $\mu$ L, 4.00 mmol), (2*R*,4*S*)-3-(*tert*-butoxycarbonyl)-2-*tert*-butyloxazolidine-4-carboxylic acid **250** (1.09 g, 4.00 mmol), DMAP (5 mol%), DCM (100 mL) and (*E*)-3-(allyloxy)prop-2-en-1-ol **218d** (228 mg, 2.00 mmol) were combined according to general procedure IV (reaction time: 16 hours) to afford the title compound without the need for further purification as a pale yellow oil (552 mg, 75%).  $[\alpha]_D^{20}$  -21 (*c* 3, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2974, 2936, 1754, 1704, 1673, 1654; <sup>1</sup>H NMR (500 MHz, d<sub>6</sub>-acetone)  $\delta_H$  0.92 (9H, s), 1.44 (9H, s), 4.14 (1H, app. t, *J* = 8.5 Hz), 4.19–4.24 (3H, m), 4.54 (2H, d, *J* = 7.9 Hz), 4.63 (1H, bs), 4.95 (1H, dt, *J* = 12.6, 7.8 Hz), 5.01 (1H, s), 5.22 (1H, dq, *J* = 10.6, 1.4 Hz), 5.29 (1H, dq, *J* = 17.3, 1.4 Hz), 5.89 (1H, ddt, *J* = 17.3, 10.6, 5.4 Hz), 6.57 (1H, d, *J* = 12.6 Hz); <sup>13</sup>C NMR (125 MHz, d<sub>6</sub>-acetone)  $\delta_C$  25.8, 28.2, 37.8, 59.7, 63.5, 68.4, 70.2, 81.2, 97.6, 98.0, 117.9, 132.7, 152.4, 155.0, 170.3; HRMS (ESI, +ve) *m/z* calcd. for C<sub>19</sub>H<sub>31</sub>NO<sub>6</sub>Na 392.2049, found: 392.2040 (M+Na)<sup>+</sup>.

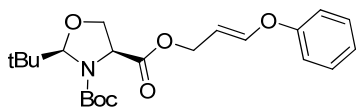


**(2*R*,4*S*)-3-*tert*-Butyl 4-((*E*)-3-(prop-2-ynyloxy)allyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate (251e)**



EDCi.HCl (767 mg, 4.00 mmol), triethylamine (560  $\mu$ L, 4.00 mmol), (2*R*,4*S*)-3-(*tert*-butoxycarbonyl)-2-*tert*-butyloxazolidine-4-carboxylic acid **250** (1.09 g, 4.00 mmol), DMAP (5 mol%), DCM (100 mL) and (*E*)-3-(prop-2-ynyloxy)prop-2-en-1-ol **218e** (224 mg, 2.00 mmol) were combined according to general procedure IV (reaction time: 2 hours). Purified on a short pad of silica (2:1 Pet:EtOAc + 1%  $\text{Net}_3$ ) to afford the title compound as a colourless oil (580 mg, 79%).  $[\alpha]_{\text{D}}^{20}$  -21 (*c* 1,  $\text{CH}_2\text{Cl}_2$ ); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 3261, 2975, 2908, 2875, 1754, 1702, 1654;  $^1\text{H}$  NMR (500 MHz,  $\text{d}_6$ -acetone)  $\delta_{\text{H}}$  0.93 (9H, s), 1.46 (9H, s), 3.09 (1H, t,  $J$  = 2.4 Hz), 4.13–4.22 (2H, m), 4.50 (2H, d,  $J$  = 2.4 Hz), 4.59 (2H, d,  $J$  = 7.8 Hz), 4.71 (1H, dd,  $J$  = 8.0, 6.2 Hz), 4.99 (1H, s), 5.11 (1H, dt,  $J$  = 12.5, 7.8 Hz), 6.71 (1H, d,  $J$  = 12.5 Hz);  $^{13}\text{C}$  NMR (125 MHz,  $\text{d}_6$ -acetone)  $\delta_{\text{C}}$  25.4, 27.5, 37.5, 56.9, 59.8, 62.6, 68.2, 76.4, 78.3, 80.3, 97.2, 99.5, 151.2, 154.8, 170.1; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{19}\text{H}_{29}\text{NO}_6\text{Na}$  390.1893, found: 390.1892 ( $\text{M}+\text{Na}$ ) $^{+}$ .

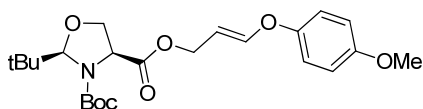
**(2*R*,4*S*)-3-*tert*-Butyl 4-((*E*)-3-phenoxyallyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate (251f)**



EDCi.HCl (383 mg, 2.00 mmol), triethylamine (280  $\mu$ L, 2.00 mmol), (2*R*,4*S*)-3-(*tert*-butoxycarbonyl)-2-*tert*-butyloxazolidine-4-carboxylic acid **250** (547 mg, 2.00 mmol), DMAP (5 mol%), DCM (50 mL) and (*E*)-3-phenoxyprop-2-en-1-ol **218f** (150 mg, 1.00 mmol) were combined according to general procedure IV (reaction time: 2 hours). Purified by flash chromatography on Brockmann Grade I Basic Alumina (4:1 Pet:EtOAc) to afford the title compound as a colourless oil (337 mg, 83%).  $[\alpha]_{\text{D}}^{20}$  -17 (*c* 1,  $\text{CH}_2\text{Cl}_2$ ); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2975, 2907, 1756, 1704, 1674, 1592;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  0.98 (9H, s), 1.49 (9H, s), 4.17 (1H, app. t,  $J$  = 8.0 Hz), 4.28 (1H, app.

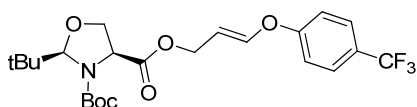
t,  $J = 8.0$  Hz), 4.65–4.72 (3H, m), 5.07 (1H, s), 5.39–5.48 (1H, m), 6.83 (1H, d,  $J = 12.2$  Hz), 7.00 (2H, d,  $J = 7.7$  Hz), 7.10 (1H, t,  $J = 7.7$  Hz), 7.33 (2H, app. t,  $J = 7.7$  Hz);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  25.9, 28.2, 37.8, 59.9, 62.2, 68.4, 81.2, 97.7, 105.1, 117.3, 123.6, 129.6, 148.7, 155.0, 156.6, 170.2; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{22}\text{H}_{31}\text{NO}_6\text{Na}$  428.2049, found: 428.2051 ( $\text{M}+\text{Na}$ ) $^{+}$ .

**(2*R*,4*S*)-3-*tert*-Butyl 4-((*E*)-3-(4-methoxyphenoxy)allyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate (251g)**



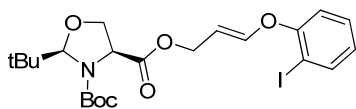
EDCI.HCl (383 mg, 2.00 mmol), triethylamine (280  $\mu\text{L}$ , 2.00 mmol), (2*R*,4*S*)-3-(*tert*-butoxycarbonyl)-2-*tert*-butyloxazolidine-4-carboxylic acid **250** (547 mg, 2.00 mmol), DMAP (5 mol%), DCM (50 mL) and (*E*)-3-(4-methoxyphenoxy)prop-2-en-1-ol **218g** (180 mg, 1.00 mmol) were combined according to general procedure IV (reaction time: 3 hours). Purified by flash chromatography (4:1 Pet:EtOAc, Brockmann Grade I Basic Alumina) to afford the title compound as a colourless oil (367 mg, 84%).  $[\alpha]_{\text{D}}^{20}$  -18 (c 1,  $\text{CH}_2\text{Cl}_2$ ); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2968, 2902, 2873, 1755, 1703, 1673, 1505;  $^1\text{H}$  NMR (500 MHz,  $\text{d}_6$ -acetone)  $\delta_{\text{H}}$  0.95 (9H, s), 1.47 (9H, s), 3.78 (3H, s), 4.15–4.25 (2H, m), 4.67 (2H, d,  $J = 7.8$  Hz), 4.74 (1H, dd,  $J = 8.1, 5.9$  Hz), 5.01 (1H, s), 5.34 (1H, dt,  $J = 12.2, 7.8$  Hz), 6.91–7.02 (5H, m);  $^{13}\text{C}$  NMR (125 MHz,  $\text{d}_6$ -acetone)  $\delta_{\text{C}}$  25.5, 27.5, 37.5, 55.0, 59.8, 62.1, 68.2, 80.4, 97.2, 104.0, 114.8, 118.3, 149.8, 150.3, 154.8, 156.1, 170.1; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{23}\text{H}_{33}\text{NO}_7\text{Na}$  458.2155, found: 458.2139 ( $\text{M}+\text{Na}$ ) $^{+}$ .

**(2*R*,4*S*)-3-*tert*-Butyl 4-((*E*)-3-(4-(trifluoromethyl)phenoxy)allyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate (251h)**



EDCI.HCl (766 mg, 4.00 mmol), triethylamine (560  $\mu$ L, 4.00 mmol), (2*R*,4*S*)-3-(*tert*-butoxycarbonyl)-2-*tert*-butyloxazolidine-4-carboxylic acid **250** (1.09 g, 4.00 mmol), DMAP (5 mol%), DCM (100 mL) and (*E*)-3-(4-(trifluoromethyl)phenoxy)prop-2-en-1-ol **218h** (436 mg, 2.00 mmol) were combined according to general procedure IV (reaction time: 2 hours) to afford the title compound without the need for further purification as a pale yellow oil (897 mg, 95%).  $[\alpha]_{\text{D}}^{20}$  -13 (*c* 3, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 2972, 2912, 2878, 1757, 1702, 1613; <sup>1</sup>H NMR (500MHz, d<sub>6</sub>-acetone)  $\delta_{\text{H}}$  0.95 (9H, s), 1.47 (9H, s), 4.16–4.26 (2H, m), 4.73–4.80 (3H, m), 5.01 (1H, s), 5.62 (1H, dt, *J* = 12.0, 7.5 Hz), 7.17 (1H, d, *J* = 12.0 Hz), 7.28 (2H, app. d, *J* = 8.7 Hz), 7.74 (2H, app. d, *J* = 8.7 Hz); <sup>13</sup>C NMR (125MHz, d<sub>6</sub>-acetone)  $\delta_{\text{C}}$  25.4, 27.5, 37.5, 59.8, 61.5, 68.1, 80.4, 97.3, 107.8, 116.8, 122.8 (q, *J* = 121.2 Hz), 124.7 (q, *J* = 33.2 Hz), 127.3 (q, *J* = 3.8 Hz), 146.7, 154.8, 159.4, 170.1; HRMS (ESI, +ve) *m/z* calcd. for C<sub>23</sub>H<sub>30</sub>F<sub>3</sub>NO<sub>6</sub>Na 496.1923, found: 496.1911 (M+Na)<sup>+</sup>.

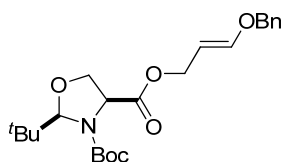
**(2*R*,4*S*)-3-*tert*-Butyl 4-((*E*)-3-(2-iodophenoxy)allyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate (**251i**)**



EDCI.HCl (383 mg, 2.00 mmol), triethylamine (280  $\mu$ L, 2.00 mmol), (2*R*,4*S*)-3-(*tert*-butoxycarbonyl)-2-*tert*-butyloxazolidine-4-carboxylic acid **250** (547 mg, 2.00 mmol), DMAP (5 mol%), DCM (50 mL) and (*E*)-3-(2-iodophenoxy)prop-2-en-1-ol **218i** (276 mg, 1.00 mmol) were combined according to general procedure (reaction time: 2 hours). Purified by flash chromatography (4:1 Pet:EtOAc, Brockmann Grade I Basic Alumina) to afford the title compound as a colourless oil (370 mg, 72%).  $[\alpha]_{\text{D}}^{20}$  -17 (*c* 2, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 2974, 2937, 2912, 1756, 1702, 1674; <sup>1</sup>H NMR (500MHz, d<sub>6</sub>-acetone)  $\delta_{\text{H}}$  0.95 (9H, s), 1.46 (9H, s), 4.16–4.26 (2H, m), 4.72 (2H, dq, *J* = 7.5, 1.0 Hz), 4.76 (1H, dd, *J* = 8.2, 5.8 Hz), 5.01 (1H, s), 5.49 (1H, dt, *J* = 12.1, 7.5 Hz), 6.96 (1H, td, *J* = 7.5, 1.3 Hz), 7.02 (1H, dt, *J* = 12.1, 1.0 Hz), 7.13 (1H, dd, *J* = 8.2, 1.3 Hz), 7.24–7.47 (1H, m), 7.89 (1H, dd, *J* = 7.5, 1.6 Hz); <sup>13</sup>C NMR (125MHz, d<sub>6</sub>-acetone)  $\delta_{\text{C}}$  25.4, 27.5, 37.5, 59.8, 61.6, 68.2, 80.4, 86.4, 97.2, 106.4, 117.2, 125.6, 130.0, 139.8, 148.1,

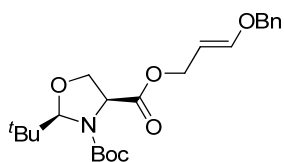
154.8, 155.8, 170.1; HRMS (ESI, +ve)  $m/z$  calcd. for  $C_{22}H_{30}INO_6Na$  554.1016, found: 554.0993 ( $M+Na$ )<sup>+</sup>.

**(±)-(*syn*)-4-((*E*)-3-(Benzyloxy)allyl) 3-*tert*-butyl 2-*tert*-butyloxazolidine-3,4-dicarboxylate (*rac*-**251j**)**



EDCI.HCl (702 mg, 3.66 mmol), triethylamine (511  $\mu$ L, 3.66 mmol), (±)-(*syn*)-3-(*tert*-butoxycarbonyl)-2-*tert*-butyloxazolidine-4-carboxylic acid *rac*-**250** (1.00 g, 3.66 mmol), DMAP (5 mol%), DCM (70 mL) and (*E*)-3-(benzyloxy)prop-2-enol **218j** (400 mg, 2.44 mmol) were combined according to general procedure IV (reaction time: 2 hours) to afford the title compound as a yellow oil without the need for further purification (955 mg, 94%). FTIR (film/ $cm^{-1}$ )  $\nu_{max}$ : 2974, 2908, 1754, 1703, 1672, 1651;  $^1H$  NMR (500MHz,  $CDCl_3$ )  $\delta_H$  0.95 (9H, s), 1.47 (9H, s), 4.12–4.19 (1H, m), 4.20–4.30 (1H, m), 4.58 (2H, d,  $J = 7.8$  Hz), 4.65 (1H, bs), 4.75 (2H, s), 5.01–5.09 (2H, m), 6.69 (1H, d,  $J = 12.6$  Hz), 7.29–7.39 (5H, m);  $^{13}C$  NMR (125MHz,  $CDCl_3$ )  $\delta_C$  25.8, 28.1, 37.9, 59.8, 63.5, 68.4, 71.4, 81.2, 97.6, 98.3, 127.5, 128.2, 128.5, 136.3, 152.6, 155.0, 170.4; HRMS (ESI, +ve)  $m/z$  calcd. for  $C_{23}H_{33}NO_6Na$  442.2206, found: 442.2201 ( $M+Na$ )<sup>+</sup>.

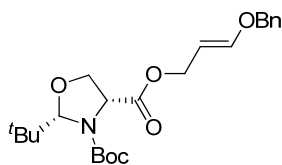
**(2*R*,4*S*)-4-((*E*)-3-(Benzyloxy)allyl) 3-*tert*-butyl 2-*tert*-butyloxazolidine-3,4-dicarboxylate (**251j**)**



EDCI.HCl (702 mg, 3.66 mmol), triethylamine (511  $\mu$ L, 3.66 mmol), (2*R*,4*S*)-3-(*tert*-butoxycarbonyl)-2-*tert*-butyloxazolidine-4-carboxylic acid **250** (1.00 g, 3.66 mmol), DMAP (5 mol%), DCM (70 mL) and (*E*)-3-(benzyloxy)prop-2-enol **218j** (400 mg, 2.44

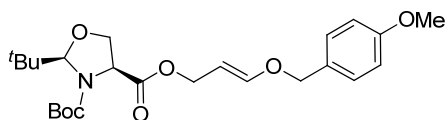
mmol) were combined according to general procedure IV (reaction time: 2 hours). Purified on a short pad of silica (2:1 Pet:EtOAc + 1%  $\text{Net}_3$ ) to afford the title compound as a colourless oil (753 mg, 74%).  $[\alpha]_{\text{D}}^{20}$  -19 (*c* 3,  $\text{CH}_2\text{Cl}_2$ ). All other data as previously stated.

**(2*S*,4*R*)-4-((*E*)-3-(Benzyloxy)allyl) 3-*tert*-butyl 2-*tert*-butyloxazolidine-3,4-dicarboxylate (*ent*-251j)**



EDCi.HCl (767 mg, 4.00 mmol), triethylamine (560  $\mu\text{L}$ , 4.00 mmol), (2*S*,4*R*)-3-(*tert*-butoxycarbonyl)-2-*tert*-butyloxazolidine-4-carboxylic acid **ent-250** (1.09 g, 4.00 mmol), DMAP (5 mol%), DCM (100 mL) and (*E*)-3-(benzyloxy)prop-2-enol **218j** (328 mg, 2.00 mmol) were combined according to general procedure IV (reaction time: 2 hours). Purified on a short pad of silica (2:1 Pet:EtOAc + 1%  $\text{Net}_3$ ) to afford the title compound as a colourless oil (654 mg, 78%).  $[\alpha]_{\text{D}}^{20}$  +19 (*c* 2,  $\text{CH}_2\text{Cl}_2$ ). All other data as previously stated.

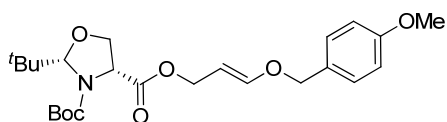
**(2*R*,4*S*)-3-*tert*-Butyl 4-((*E*)-3-(4-methoxybenzyloxy)allyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate (251k)**



EDCi.HCl (383 mg, 2.00 mmol), triethylamine (280  $\mu\text{L}$ , 2.00 mmol), (2*R*,4*S*)-3-(*tert*-butoxycarbonyl)-2-*tert*-butyloxazolidine-4-carboxylic acid **250** (547 mg, 2.00 mmol), DMAP (5 mol%), DCM (50 mL) and (*E*)-3-(4-methoxybenzyloxy)prop-2-en-1-ol **218k** (194 mg, 1.00 mmol) were combined according to the general procedure IV (reaction time: 30 minutes), purified by flash chromatography (4:1 Pet:EtOAc, Brockmann Grade I Basic Alumina) to afford the title compound as a colourless oil (227 mg, 51%).  $[\alpha]_{\text{D}}^{20}$  -17.0 (*c* 2.0,  $\text{CH}_2\text{Cl}_2$ ); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2959, 2915, 2849, 1753, 1703, 1672,

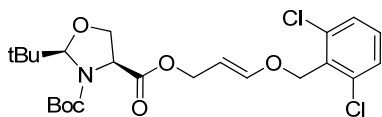
1651, 1614, 1515;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  0.96 (9H, s), 1.48 (9H, s), 3.81 (3H, s), 4.15 (1H, app. t,  $J = 7.6$  Hz), 4.22–4.28 (1H, m), 4.59 (2H, d,  $J = 7.7$  Hz), 4.66 (1H, app. t,  $J = 7.6$  Hz), 4.71 (2H, s), 5.02–5.12 (2H, m), 6.66 (1H, d,  $J = 12.6$  Hz), 6.90 (2H, d,  $J = 8.5$  Hz), 7.25 (2H, d,  $J = 8.5$  Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  25.8, 28.2, 37.8, 55.2, 59.9, 63.4, 68.4, 71.4, 81.1, 97.7, 98.5, 114.0, 128.6, 129.1, 152.5, 155.0, 159.7, 170.3; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{24}\text{H}_{35}\text{NO}_7\text{Na}$  472.2311, found: 472.2286 ( $\text{M}+\text{Na}$ ) $^+$ .

**(2*S*,4*R*)-3-*tert*-Butyl 4-((*E*)-3-(4-methoxybenzyloxy)allyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate (*ent*-251k)**



EDCi.HCl (612 mg, 3.19 mmol), triethylamine (445  $\mu\text{L}$ , 3.19 mmol), (2*S*,4*R*)-3-(*tert*-butoxycarbonyl)-2-*tert*-butyloxazolidine-4-carboxylic acid *ent*-**250** (872 mg, 3.19 mmol), DMAP (5 mol%), DCM (50 mL) and (*E*)-3-(4-methoxybenzyloxy)prop-2-en-1-ol **218k** (370 mg, 1.60 mmol) were combined according to general procedure IV (reaction time: 30 minutes). Purified by flash chromatography (2:1 Pet/EtOAc + 1%  $\text{Et}_3\text{N}$ ) to afford the title compound as a colourless oil (719 mg, 100%).  $[\alpha]_{\text{D}}^{20} +17.1$  (c 2.1,  $\text{CH}_2\text{Cl}_2$ ). All other data as previously stated.

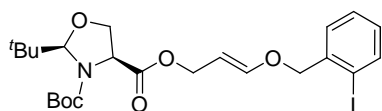
**(2*R*,4*S*)-3-*tert*-Butyl 4-((*E*)-3-(2,6-dichlorobenzyloxy)allyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate (**251l**)**



EDCi.HCl (383 mg, 2.00 mmol), triethylamine (280  $\mu\text{L}$ , 2.00 mmol), (2*R*,4*S*)-3-(*tert*-butoxycarbonyl)-2-*tert*-butyloxazolidine-4-carboxylic acid **250** (547 mg, 2.00 mmol), DMAP (5 mol%), DCM (50 mL) and (*E*)-methyl 3-(2,6-dichlorobenzyloxy)acrylate **218l** (233 mg, 1.00 mmol) were combined according to general procedure IV (reaction

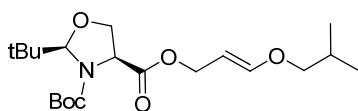
time: 50 minutes). Purified by flash chromatography (4:1 Pet:EtOAc) to afford the title compound as a colourless oil (291 mg, 60%).  $[\alpha]_D^{20}$  -15 (*c* 2.0, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2975, 2908, 1753, 1703, 1673, 1651, 1583, 1565; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_H$  0.95 (9H, s), 1.47 (9H, s), 4.15 (1H, app. t, *J* = 8.0 Hz), 4.25 (1H, dd, *J* = 8.0, 6.5 Hz), 4.60 (2H, d, *J* = 7.7 Hz), 4.67 (1H, app. t, *J* = 8.0 Hz), 5.02 (2H, s), 5.04 (1H, s), 5.09–5.17 (1H, m), 6.71 (1H, d, *J* = 12.5 Hz), 7.21 (1H, t, *J* = 8.1 Hz), 7.33 (2H, d, *J* = 8.1 Hz); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_C$  25.9, 28.2, 37.8, 59.9, 63.1, 66.2, 68.4, 81.1, 97.7, 98.7, 128.4, 130.4, 131.8, 136.9, 152.3, 154.9, 170.3; HRMS (ESI, +ve) *m/z* calcd. for C<sub>23</sub>H<sub>31</sub>NC<sub>2</sub>O<sub>6</sub>Na 510.1426, found: 510.1405 (M+Na)<sup>+</sup>.

**(2*R*,4*S*)-3-*tert*-Butyl 4-((*E*)-3-(2-iodobenzyloxy)allyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate (251m)**



EDCi.HCl (383 mg, 2.00 mmol), triethylamine (280  $\mu$ L, 2.00 mmol), (2*R*,4*S*)-3-(*tert*-butoxycarbonyl)-2-*tert*-butyloxazolidine-4-carboxylic acid **250** (547 mg, 2.00 mmol), DMAP (5 mol%), DCM (50 mL) and (*E*)-3-(2-iodobenzyloxy)prop-2-en-1-ol **218m** (290 mg, 1.00 mmol) were combined according to general procedure IV (reaction time: 1 hour) to afford the crude title compound as a pale yellow oil (quant.) which was taken forward in its crude form.

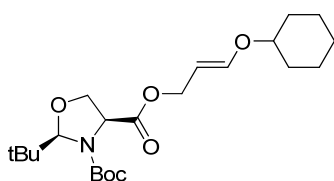
**(2*R*,4*S*)-3-*tert*-Butyl 4-((*E*)-3-isobutoxyallyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate (251n)**



EDCi.HCl (383 mg, 2.00 mmol), triethylamine (280  $\mu$ L, 2.00 mmol), (2*R*,4*S*)-3-(*tert*-butoxycarbonyl)-2-*tert*-butyloxazolidine-4-carboxylic acid **250** (547 mg, 2.00 mmol), DMAP (5 mol%), DCM (50 mL) and (*E*)-3-isobutoxyprop-2-en-1-ol **218n** (130 mg, 1.00 mmol) were combined according to general procedure IV (reaction time: 20

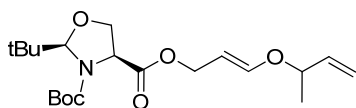
minutes) to afford the crude title compound as a pale yellow oil (quant.) which was taken forward in its crude form.

**(2*R*,4*S*)-3-*tert*-Butyl 4-((*E*)-3-(cyclohexyloxy)allyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate (251o)**



EDCi.HCl (383 mg, 2.00 mmol), triethylamine (280  $\mu$ L, 2.00 mmol), (2*R*,4*S*)-3-(*tert*-butoxycarbonyl)-2-*tert*-butyloxazolidine-4-carboxylic acid **250** (547 mg, 2.00 mmol), DMAP (5 mol%), DCM (50 mL) and (*E*)-3-(cyclohexyloxy)prop-2-en-1-ol **218o** (156 mg, 1.00 mmol) were combined according to general procedure IV (reaction time: 2 hours) to afford the crude title compound as a yellow oil (quant.) which was taken forward in its crude form.

**(2*R*,4*S*)-4-((*E*)-3-(But-3-en-2-yloxy)allyl) 3-*tert*-butyl 2-*tert*-butyloxazolidine-3,4-dicarboxylate (251p)**

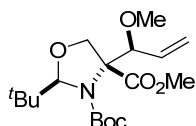


EDCi.HCl (383 mg, 2.00 mmol), triethylamine (280  $\mu$ L, 2.00 mmol), (2*R*,4*S*)-3-(*tert*-butoxycarbonyl)-2-*tert*-butyloxazolidine-4-carboxylic acid **250** (547 mg, 2.00 mmol), DMAP (5 mol%), DCM (50 mL) and (*E*)-3-(but-3-en-2-yloxy)prop-2-en-1-ol **218p** (128 mg, 1.00 mmol) were combined according to general procedure IV (reaction time: 10 minutes) to afford the title compound as a yellow oil (383 mg, 83%).  $[\alpha]_D^{20}$  -23 (*c* 2.0, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2977, 2933, 2872, 1758, 1709, 1672; <sup>1</sup>H NMR (500MHz, d<sub>6</sub>-acetone)  $\delta_H$  0.94 (9H, s), 1.29 (3H, d, *J* = 6.5 Hz), 1.46 (9H, s), 4.12–4.21 (2H, m), 4.43 (1H, quin., *J* = 6.4 Hz), 4.55 (2H, d, *J* = 7.8 Hz), 4.69 (1H, app. t, *J* = 7.0 Hz), 4.98–5.06 (2H, m), 5.15 (1H, dd, *J* = 10.6, 1.0 Hz), 5.26 (1H, dd, *J* = 17.3, 1.0 Hz), 5.83 (1H, ddd, *J* = 17.3, 10.6, 6.4 Hz), 6.61 (1H, d, *J* = 12.4 Hz); <sup>13</sup>C NMR (125MHz,



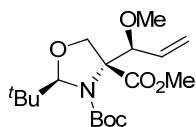
$d_6$ -acetone)  $\delta_C$  20.2, 25.5, 27.5, 37.5, 59.8, 63.0, 68.2, 77.2, 80.3, 97.2, 99.2, 115.4, 139.0, 151.7, 154.7, 170.1; HRMS (ESI, +ve)  $m/z$  calcd. for  $C_{20}H_{33}NO_6Na$  406.2206, found: 406.2212 ( $M+Na$ )<sup>+</sup>.

**(±)-(anti)-3-*tert*-Butyl 4-methyl 2-*tert*-butyl-4-(1-methoxyallyl)oxazolidine-3,4-dicarboxylate (*rac*-252a)**



(±)-(syn)-3-*tert*-Butyl 4-((*E*)-3-methoxyallyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate **rac-251a** (500 mg, 1.46 mmol), TMSCl (556  $\mu$ L, 4.37 mmol), LHMDs (1M, 4.37 mL, 4.37 mmol) and THF (5.0 mL) were combined according to general procedure VII (reaction time: 18 hours). Purified by flash chromatography (8:1 Pet/EtOAc) to afford the methyl ester as a colourless oil (419 mg, 81%, dr >99:1). FTIR (film/cm<sup>-1</sup>)  $\nu_{max}$ : 2979, 2957, 2907, 1743, 1702; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>, 328K)  $\delta_H$  0.95 (9H, s), 1.52 (9H, s), 3.29 (3H, s), 3.74 (3H, s), 4.18 (1H, d,  $J$  = 8.5 Hz), 4.35 (1H, d,  $J$  = 8.5 Hz), 4.83 (1H, bs), 5.14 (1H, s), 5.32–5.40 (2H, m), 5.64–5.75 (1H, m); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_C$  26.1, 28.2, 38.1, 52.3, 56.8, 69.2, 72.3, 78.4, 80.8, 98.0, 120.1, 133.6, 153.8, 171.0; HRMS (ESI, +ve)  $m/z$  calcd. for  $C_{18}H_{31}NO_6Na$  380.2049, found: 380.2032 ( $M+Na$ )<sup>+</sup>.

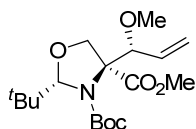
**(2*R*,4*R*)-3-*tert*-Butyl 4-methyl 2-*tert*-butyl-4-((*S*)-1-methoxyallyl)oxazolidine-3,4-dicarboxylate (252a)**



(2*R*,4*S*)-3-*tert*-Butyl 4-((*E*)-3-methoxyallyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate **251a** (476 mg, 1.39 mmol), TMSCl (529  $\mu$ L, 4.16 mmol), LHMDs (1M, 4.16 mL, 4.16 mmol) and THF (4.75 mL) were combined according to general procedure VII (reaction time: 18 hours). Purification by flash chromatography (8:1 Pet/EtOAc) affords the

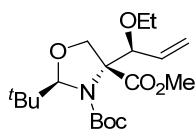
methyl ester as a colourless oil (388 mg, 78%, dr >99:1).  $[\alpha]_D^{20}$  -12.0 (*c* 2.0, CH<sub>2</sub>Cl<sub>2</sub>). All other data as previously stated.

**(2*S*,4*S*)-3-*tert*-Butyl 4-methyl 2-*tert*-butyl-4-((*R*)-1-methoxyallyl)oxazolidine-3,4-dicarboxylate (*ent*-252a)**



(2*S*,4*R*)-3-*tert*-Butyl 4-((*E*)-3-methoxyallyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate *ent*-251a (247 mg, 0.719 mmol), TMSCl (275  $\mu$ L, 2.16 mmol), LHMDs (1M, 2.16 mL, 2.16 mmol) and THF (2.5 mL) were combined according to general procedure VII (reaction time: 18 hours). Purification by flash chromatography (8:1 Pet/EtOAc) affords the methyl ester as a colourless oil (213 mg, 83%, dr >99:1).  $[\alpha]_D^{20}$  +12.1 (*c* 1.9, CH<sub>2</sub>Cl<sub>2</sub>). All other data as previously stated.

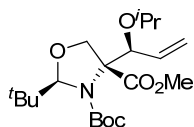
**(2*R*,4*R*)-3-*tert*-Butyl 4-methyl 2-*tert*-butyl-4-((*S*)-1-ethoxyallyl)oxazolidine-3,4-dicarboxylate (252b)**



(2*R*,4*S*)-3-*tert*-Butyl 4-((*E*)-3-ethoxyallyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate 251b (109 mg, 0.305 mmol), TMSCl (116  $\mu$ L, 0.915 mmol), LHMDs (1M, 915  $\mu$ L, 0.915 mmol) and THF (1.10 mL) were combined according to general procedure VII (reaction time: 18 hours). Purification by flash chromatography (15:1 Pet/EtOAc) affords the methyl ester as a colourless oil (95 mg, 84%, dr >99:1).  $[\alpha]_D^{20}$  +5 (*c* 2.0, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 2978, 2903, 1743, 1710; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 328K)  $\delta_{\text{H}}$  0.94 (9H, s), 1.16 (3H, t, *J* = 7.2 Hz), 1.49 (9H, s), 3.32 (1H, app. qu, *J* = 7.2 Hz), 3.53 (1H, app. qu, *J* = 7.2 Hz), 3.72 (3H, s), 4.21 (1H, d, *J* = 8.3 Hz), 4.30 (1H, d, *J* = 8.3 Hz), 4.90 (1H, bs), 5.12 (1H, s), 5.29 (1H, d, *J* = 10.5 Hz), 5.34 (1H, d, *J* = 17.2 Hz), 5.67–5.79 (1H, m); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, 328K)  $\delta_{\text{C}}$  15.2, 26.2, 28.2, 38.3,

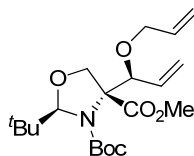
52.0, 64.5, 70.0, 72.2, 77.9, 80.6, 98.3, 119.0, 134.8, 153.6, 171.0; HRMS (ESI, +ve)  $m/z$  calcd. for  $C_{19}H_{33}NO_6Na$  394.2206, found: 394.2201 ( $M+Na$ )<sup>+</sup>.

**(2*R*,4*R*)-3-*tert*-Butyl 4-methyl 2-*tert*-butyl-4-((*S*)-1-isopropoxyallyl)oxazolidine-3,4-dicarboxylate (252c)**



(2*R*,4*S*)-3-*tert*-Butyl 4-((*E*)-3-isopropoxyallyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate **251c** (77 mg, 0.207 mmol), TMSCl (79  $\mu$ L, 0.621 mmol), LHMDS (1M, 621  $\mu$ L, 0.621 mmol) and THF (0.77 mL) were combined according to general procedure VII (reaction time: 18 hours). Purification by flash chromatography (10:1 Pet/EtOAc) affords the methyl ester as a colourless oil (56 mg, 70%, dr >99:1).  $[\alpha]_D^{20} +12$  ( $c$  2.0,  $CH_2Cl_2$ ); FTIR (film/ $cm^{-1}$ )  $\nu_{max}$ : 2976, 2908, 1744, 1705;  $^1H$  NMR (500 MHz,  $CDCl_3$ , 328K)  $\delta_H$  0.97 (9H, s), 1.12 (3H, d,  $J$  = 6.1 Hz), 1.14 (3H, d,  $J$  = 6.1 Hz), 1.50 (9H, s), 3.68–3.74 (4H, m), 4.26–4.32 (2H, m), 5.03 (1H, bs), 5.13 (1H, s), 5.27 (1H, d,  $J$  = 10.6 Hz), 5.40 (1H, d,  $J$  = 17.3 Hz), 5.85 (1H, ddd,  $J$  = 17.3, 10.6, 6.9 Hz);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ , 328K)  $\delta_C$  22.1, 23.2, 26.5, 28.3, 38.6, 51.9, 70.4, 70.7, 72.3, 76.1, 80.9, 98.3, 118.9, 136.5, 153.1, 171.0; HRMS (ESI, +ve)  $m/z$  calcd. for  $C_{20}H_{35}NO_6Na$  408.2362, found: 408.2366 ( $M+Na$ )<sup>+</sup>.

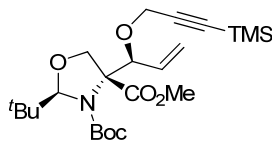
**(2*R*,4*R*)-3-*tert*-Butyl 4-methyl 2-*tert*-butyl-4-((*S*)-1-(allyloxy)allyl)oxazolidine-3,4-dicarboxylate (252d)**



(2*R*,4*S*)-3-*tert*-Butyl 4-((*E*)-3-(allyloxy)allyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate **251d** (227 mg, 0.610 mmol), TMSCl (234  $\mu$ L, 1.84 mmol), LHMDS (1M, 1.84 mL, 1.84 mmol) and THF (2.30 mL) were combined according to general procedure VII

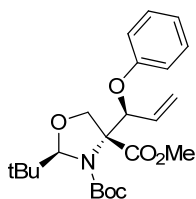
(reaction time: 18 hours). Purification by flash chromatography (10:1 Pet/EtOAc) affords the methyl ester as a colourless oil (165 mg, 71%, dr >99:1).  $[\alpha]_D^{20} +6$  ( $c$  2.0,  $\text{CH}_2\text{Cl}_2$ ); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2979, 2960, 2909, 1743, 1709;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 328K)  $\delta_{\text{H}}$  0.94 (9H, s), 1.48 (9H, s), 3.73 (3H, s), 3.85 (1H, ddt,  $J = 12.6, 5.2, 1.6$  Hz), 4.01 (1H, dd,  $J = 12.6, 5.2$  Hz), 4.24 (1H, d,  $J = 8.5$  Hz), 4.34 (1H, d,  $J = 8.5$  Hz), 4.99 (1H, bs), 5.10 (1H, dq,  $J = 17.3, 1.4$  Hz), 5.13 (1H, s), 5.24 (1H, dq,  $J = 10.4, 1.4$  Hz), 5.32 (1H, app. dt,  $J = 10.4, 1.4$  Hz), 5.36 (1H, app. dt,  $J = 17.3, 1.4$  Hz), 5.72 (1H, ddd,  $J = 17.3, 10.4, 6.9$  Hz), 5.88 (1H, ddt,  $J = 17.3, 10.5, 5.2$  Hz);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , 328K)  $\delta_{\text{C}}$  26.2, 28.2, 38.3, 52.0, 69.6, 69.9, 72.3, 77.6, 80.8, 98.3, 115.7, 119.7, 134.3, 134.7, 153.6, 170.9; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{20}\text{H}_{33}\text{NO}_6\text{Na}$  406.2206, found: 406.2200 ( $\text{M}+\text{Na}$ ) $^+$ .

**(2R,4R)-3-tert-Butyl 4-methyl 2-tert-butyl-4-((S)-1(3-(trimethylsilyl)prop-2-ynyloxy)allyl)oxazolidine-3,4-dicarboxylate (252e)**



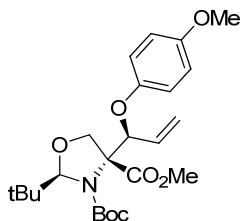
(2R,4S)-3-tert-Butyl 4-((E)-3-(prop-2-ynyloxy)allyl) 2-tert-butylloxazolidine-3,4-dicarboxylate **251e** (100 mg, 0.272 mmol),  $\text{TMSCl}$  (104  $\mu\text{L}$ , 0.816 mmol),  $\text{LHMDS}$  (1M, 816  $\mu\text{L}$ , 0.816 mmol) and THF (1.00 mL) were combined according to general procedure VII (reaction time: 18 hours). Purification by flash chromatography (10:1 Pet/EtOAc) affords the methyl ester as a colourless oil (94 mg, 76%, dr >99:1).  $[\alpha]_D^{20} -7$  ( $c$  2.0,  $\text{CH}_2\text{Cl}_2$ ); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2981, 2959, 2905, 1744, 1707;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 328K)  $\delta_{\text{H}}$  0.17 (9H, s), 0.94 (9H, s), 1.52 (9H, s), 3.73 (3H, s), 4.09 (2H, q,  $J = 15.1$  Hz), 4.20 (1H, d,  $J = 8.4$  Hz), 4.37 (1H, d,  $J = 8.4$  Hz), 5.00 (1H, d,  $J = 6.3$  Hz), 5.14 (1H, s), 5.34 (1H, d,  $J = 10.4$  Hz), 5.41 (1H, d,  $J = 17.2$  Hz), 5.65–5.76 (1H, m);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , 328K)  $\delta_{\text{C}}$  -0.3, 26.2, 28.2, 38.2, 52.1, 57.5, 69.8, 72.3, 78.0, 81.0, 91.1, 98.1, 101.8, 120.6, 133.5, 153.6, 170.7; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{23}\text{H}_{39}\text{NO}_6\text{SiNa}$  476.2444, found: 476.2434 ( $\text{M}+\text{Na}$ ) $^+$ .

**(2*R*,4*R*)-3-*tert*-Butyl 4-methyl 2-*tert*-butyl-4-((*S*)-1-phenoxyallyl)oxazolidine-3,4-dicarboxylate (252f)**



(2*R*,4*S*)-3-*tert*-Butyl 4-((*E*)-3-phenoxyallyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate **251f** (200 mg, 0.493 mmol), TMSCl (188  $\mu$ L, 1.48 mmol), LHMDs (1M, 1.48 mL, 1.48 mmol) and THF (2.00 mL) were combined according to general procedure VII (reaction time: 18 hours). Purification by flash chromatography (10:1 Pet/EtOAc) affords the methyl ester as a colourless oil (160 mg, 77%, dr >99:1).  $[\alpha]_D^{20} +57$  (*c* 2.0, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2979, 2957, 2908, 1743, 1721; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 328K)  $\delta_H$  1.03 (9H, s), 1.14 (9H, s), 3.81 (3H, s), 4.34 (1H, d, *J* = 8.7 Hz), 4.45 (1H, d, *J* = 8.7 Hz), 5.29 (1H, s), 5.37 (1H, app. dt, *J* = 10.9, 1.4 Hz), 5.41 (1H, app. dt, *J* = 17.4, 1.4 Hz), 5.82 (1H, bs), 6.05 (1H, ddd, *J* = 17.4, 10.9, 4.5 Hz), 6.88–6.94 (3H, m), 7.19–7.24 (2H, m); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, 328K)  $\delta_C$  26.4, 27.7, 38.7, 46.3, 52.3, 70.9, 71.8, 81.2, 98.7, 115.8, 119.3, 121.1, 129.0, 133.7, 153.4, 157.9, 170.9; HRMS (ESI, +ve) *m/z* calcd. for C<sub>23</sub>H<sub>33</sub>NO<sub>6</sub>Na 442.2206, found: 442.2177 (M+Na)<sup>+</sup>.

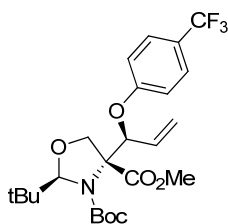
**(2*R*,4*R*)-3-*tert*-Butyl 4-methyl 2-*tert*-butyl-4-((*S*)-1-(4-methoxyphenoxy)allyl)oxazolidine-3,4-dicarboxylate (252g)**



(2*R*,4*S*)-3-*tert*-Butyl 4-((*E*)-3-(4-methoxyphenoxy)allyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate **251g** (200 mg, 0.459 mmol), TMSCl (176  $\mu$ L, 1.38 mmol), LHMDs (1M, 1.38 mL, 1.38 mmol) and THF (2.00 mL) were combined according to general procedure VII (reaction time: 18 hours). Purification by flash chromatography (10:1

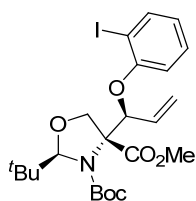
Pet/EtOAc) affords the methyl ester as a colourless oil (141 mg, 68%, dr >99:1).  $[\alpha]_{\text{D}}^{20} +31$  ( $c$  3.0,  $\text{CH}_2\text{Cl}_2$ ); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2981, 2956, 2908, 2836, 1742, 1709, 1506;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 328K)  $\delta_{\text{H}}$  1.01 (9H, s), 1.16 (9H, s), 3.73 (3H, s), 3.79 (3H, s), 4.32 (1H, d,  $J = 8.6$  Hz), 4.42 (1H, d,  $J = 8.6$  Hz), 5.27 (1H, s), 5.33 (1H, d,  $J = 10.8$  Hz), 5.39 (1H, d,  $J = 17.4$  Hz), 5.70 (1H, bs), 6.05 (1H, ddd,  $J = 17.4, 10.8, 4.1$  Hz), 6.76 (2H, app. d,  $J = 9.1$  Hz), 6.84 (2H, app. d,  $J = 9.1$  Hz);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , 328K)  $\delta_{\text{C}}$  26.4, 27.8, 38.7, 52.2, 55.7, 70.8, 71.8, 77.1, 81.1, 98.6, 114.4, 116.7, 119.3, 134.0, 152.1, 153.4, 154.3, 170.9; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{24}\text{H}_{35}\text{NO}_7\text{Na}$  472.2311, found: 472.2309 ( $\text{M}+\text{Na}$ ) $^+$ .

**(2*R*,4*R*)-3-*tert*-Butyl 4-methyl 2-*tert*-butyl-4-((*S*)-1-(4-(trifluoromethyl)phenoxy)allyl) oxazolidine-3,4-dicarboxylate (252h)**



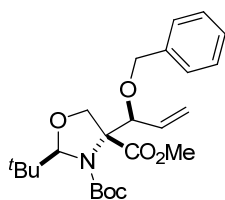
(2*R*,4*S*)-3-*tert*-Butyl 4-((*E*)-3-(4-(trifluoromethyl)phenoxy)allyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate **251h** (150 mg, 0.317 mmol),  $\text{TMSCl}$  (121  $\mu\text{L}$ , 0.951 mmol),  $\text{LHMDS}$  (1M, 951  $\mu\text{L}$ , 0.951 mmol) and THF (1.50 mL) were combined according to general procedure VII (reaction time: 18 hours). Purification by flash chromatography (10:1 Pet/EtOAc) affords the methyl ester as a colourless oil (133 mg, 73%, dr >99:1).  $[\alpha]_{\text{D}}^{20} +47$  ( $c$  2.0,  $\text{CH}_2\text{Cl}_2$ ); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2980, 2956, 2913, 1741, 1710, 1614;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 328K)  $\delta_{\text{H}}$  1.03 (9H, s), 1.14 (9H, s), 3.82 (3H, s), 4.35 (1H, d,  $J = 8.8$  Hz), 4.44 (1H, d,  $J = 8.8$  Hz), 5.26 (1H, s), 5.34–5.43 (2H, m), 5.91 (1H, bs), 6.00–6.10 (1H, m), 6.99 (2H, app. d,  $J = 8.6$  Hz), 7.50 (2H, app. d,  $J = 8.6$  Hz);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , 328K)  $\delta_{\text{C}}$  26.4, 27.7, 38.7, 52.4, 70.8, 71.7, 81.4, 98.7, 115.8, 119.6, 123.2, 123.6 (q,  $J = 32.7$  Hz), 125.4, 126.6 (q,  $J = 3.8$  Hz), 132.9, 153.3, 160.3, 170.6; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{24}\text{H}_{32}\text{F}_3\text{NO}_6\text{Na}$  510.2079, found: 510.2085 ( $\text{M}+\text{Na}$ ) $^+$ .

**(2*R*,4*R*)-3-*tert*-Butyl 4-methyl 2-*tert*-butyl-4-((*S*)-1-(2-iodophenoxy)allyl) oxazolidine-3,4-dicarboxylate (**252i**)**



(2*R*,4*S*)-3-*tert*-Butyl 4-((*E*)-3-(2-iodophenoxy)allyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate **251i** (166 mg, 0.312 mmol), TMSCl (120  $\mu$ L, 0.937 mmol), LHMDS (1M, 937  $\mu$ L, 0.937 mmol) and THF (1.70 mL) were combined according to general procedure VII (reaction time: 18 hours). Purification by flash chromatography (15:1 Pet/EtOAc) affords the methyl ester as a colourless oil (99 mg, 58%, dr >99:1).  $[\alpha]_D^{20} +19$  (*c* 3.0, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2978, 2958, 2903, 1742, 1704; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 328K)  $\delta_H$  0.99 (9H, s), 1.20 (9H, s), 3.82 (3H, s), 4.50 (1H, d, *J* = 8.6 Hz), 4.55 (1H, d, *J* = 8.6 Hz), 5.27–5.35 (2H, m), 5.47 (1H, s), 5.86 (1H, ddd, *J* = 16.6, 10.8, 5.2 Hz), 6.18 (1H, bs), 6.66 (1H, t, *J* = 7.6 Hz), 6.79 (1H, d, *J* = 8.3 Hz), 7.13–7.28 (1H, m), 7.75 (1H, d, *J* = 7.6 Hz); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, 328K)  $\delta_C$  26.3, 27.7, 38.1, 52.3, 69.9, 71.8, 81.2, 86.4, 98.4, 113.3, 120.3, 122.6, 128.1, 129.0, 132.2, 139.3, 153.4, 155.5, 170.7; HRMS (ESI, +ve) *m/z* calcd. for C<sub>23</sub>H<sub>32</sub>INO<sub>6</sub>Na 568.1172, found: 568.1167 (M+Na)<sup>+</sup>. X-Ray: Structure deposited with CCDC (CCDC 812147)

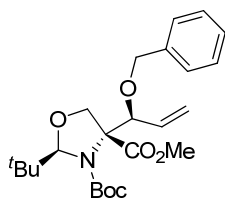
**(±)-(anti)-3-*tert*-Butyl 4-methyl 4-(1-(benzyloxy)allyl)-2-*tert*-butyloxazolidine-3,4-dicarboxylate (*rac*-**252j**)**



(±)- (syn)-4-((*E*)-3-(Benzyloxy)allyl) 3-*tert*-butyl 2-*tert*-butyloxazolidine-3,4-dicarboxylate *rac*-**251j** (232 mg, 0.553 mmol), TMSCl (211  $\mu$ L, 1.66 mmol), LHMDS (1M, 1.66 mL, 1.66 mmol) and THF (2.30 mL) were combined according to general

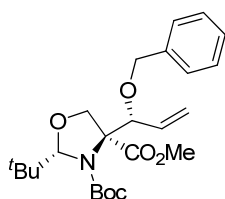
procedure VII (reaction time: 18 hours). Purification by flash chromatography (15:1 Pet/EtOAc) affords the methyl ester as a colourless oil (185 mg, 73%, dr >99:1). FTIR (film/cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 2981, 2958, 2903, 1741, 1708; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 328K)  $\delta_{\text{H}}$  0.97 (9H, s), 1.41 (9H, s), 3.76 (3H, s), 4.30 (1H, d,  $J$  = 8.5 Hz), 4.36–4.49 (2H, m), 4.54 (1H, d,  $J$  = 8.5 Hz), 5.12–5.20 (2H, m), 5.35 (1H, d,  $J$  = 10.4 Hz), 5.41 (1H, d,  $J$  = 17.2 Hz), 5.78 (1H, ddd,  $J$  = 17.2, 10.4, 7.0 Hz), 7.22–7.28 (1H, m), 7.29–7.38 (4H, m); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, 328K)  $\delta_{\text{C}}$  26.2, 28.1, 38.3, 52.4, 70.1, 70.2, 72.4, 81.0, 97.6, 98.1, 120.3, 126.8, 127.2, 128.4, 134.0, 138.5, 153.7, 171.1; HRMS (ESI, +ve)  $m/z$  calcd. for C<sub>24</sub>H<sub>35</sub>NO<sub>6</sub>Na 456.2362, found: 456.2340 (M+Na)<sup>+</sup>.

**(2*R*,4*R*)-3-*tert*-Butyl 4-methyl 4-((*S*)-1-(benzyloxy)allyl)-2-*tert*-butyloxazolidine-3,4-dicarboxylate (252j)**



(2*R*,4*S*)-3-*tert*-Butyl 4-((*E*)-3-(benzyloxy)allyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate **251j** (247 mg, 0.589 mmol), TMSCl (225  $\mu$ L, 1.77 mmol), LHMDs (1M, 1.77 mL, 1.77 mmol) and THF (2.50 mL) were combined according to general procedure VII (reaction time: 18 hours). Purification by flash chromatography (15:1 Pet/EtOAc) affords the methyl ester as a colourless oil (185 mg, 73%, dr >99:1).  $[\alpha]_{\text{D}}^{20} \pm 0$  ( $c$  1.0, CH<sub>2</sub>Cl<sub>2</sub>). All other data as previously stated.

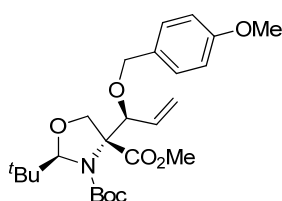
**(2*S*,4*S*)-3-*tert*-Butyl 4-methyl 4-((*R*)-1-(benzyloxy)allyl)-2-*tert*-butyloxazolidine-3,4-dicarboxylate (*ent*-252j)**





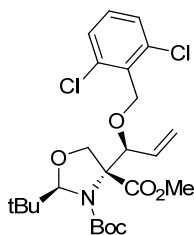
(2*S*,4*R*)-3-*tert*-Butyl 4-((*E*)-3-(benzyloxy)allyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate **ent-251j** (200 mg, 0.480 mmol), TMSCl (183  $\mu$ L, 1.44 mmol), LHMDs (1M, 1.44 mL, 1.44 mmol) and THF (2.00 mL) were combined according to general procedure VII (reaction time: 18 hours). Purification by flash chromatography (15:1 Pet/EtOAc) affords the methyl ester as a colourless oil (149 mg, 72%, dr >99:1).  $[\alpha]_D^{20} \pm 0$  (*c* 1.0, CH<sub>2</sub>Cl<sub>2</sub>). All other data as previously stated.

**(2*R*,4*R*)-3-*tert*-Butyl 4-methyl 2-*tert*-butyl-4-((*S*)-1-(4-methoxybenzyloxy)allyl) oxazolidine-3,4-dicarboxylate (252k)**



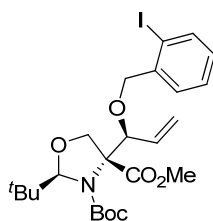
(2*R*,4*S*)-3-*tert*-Butyl 4-((*E*)-3-(4-methoxybenzyloxy)allyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate **251k** (118 mg, 0.260 mmol), TMSCl (100  $\mu$ L, 0.78 mmol), LHMDs (1M, 780  $\mu$ L, 0.78 mmol) and THF (1.20 mL) were combined according to general procedure VII (reaction time: 18 hours). Purification by flash chromatography (8:1 Pet/EtOAc) affords the methyl ester as a colourless oil (90 mg, 75%, dr >99:1).  $[\alpha]_D^{20} - 6.0$  (*c* 2.0, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2981, 2957, 2908, 1743, 1707; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 328K)  $\delta_H$  0.96 (9H, s), 1.44 (9H, s), 3.75 (3H, s), 3.80 (3H, s), 4.28 (1H, d, *J* = 8.5 Hz), 4.34-4.39 (2H, m), 4.47 (1H, d, *J* = 11.1 Hz), 5.08-5.18 (2H, m), 5.34 (1H, app. dt, *J* = 10.5, 1.4 Hz), 5.40 (1H, d, *J* = 17.2 Hz), 5.78 (1H, ddd, *J* = 17.2, 10.5, 6.8 Hz), 6.86 (2H, app. d, *J* = 8.7 Hz), 7.23 (2H, app. d, *J* = 8.7 Hz); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, 328K)  $\delta_C$  26.3, 28.2, 38.3, 52.0, 55.2, 70.3, 72.4, 78.0, 80.9, 98.3, 113.7, 119.8, 128.4, 130.0, 130.7, 134.3, 153.6, 159.0, 171.0; HRMS (ESI, +ve) *m/z* calcd. for C<sub>25</sub>H<sub>37</sub>NO<sub>7</sub>Na 486.2468, found: 486.2442 (M+Na)<sup>+</sup>.

**(2*R*,4*R*)-3-*tert*-Butyl 4-methyl 2-*tert*-butyl-4-((*S*)-1-(2,6-dichlorobenzyloxy)allyl) oxazolidine-3,4-dicarboxylate (252l)**



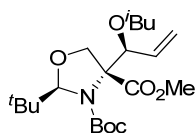
(2*R*,4*S*)-3-*tert*-Butyl 4-((*E*)-3-(2,6-dichlorobenzyloxy)allyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate **251l** (215 mg, 0.440 mmol), TMSCl (168  $\mu$ L, 1.32 mmol), LHMDs (1M, 1.32 mL, 1.32 mmol) and THF (2.20 mL) were combined according to general procedure VII (reaction time: 18 hours). Purification by flash chromatography (10:1 Pet/EtOAc) affords the methyl ester as a colourless oil (154 mg, 70%, dr 93:7). FTIR (film/cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 2979, 2957, 2908, 1743, 1707; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>, 328K)  $\delta_{\text{H}}$  Major Diastereomer 0.96 (9H, s), 1.48 (9H, s), 3.73 (3H, s), 4.27 (1H, d,  $J$  = 8.7 Hz), 4.33 (1H, d,  $J$  = 8.7 Hz), 4.76 (1H, d,  $J$  = 10.8 Hz), 4.81 (1H, d,  $J$  = 10.8 Hz), 5.10–5.19 (2H, m), 5.24 (1H, d,  $J$  = 10.3 Hz), 5.38 (1H, d,  $J$  = 17.2 Hz), 5.77 (1H, ddd,  $J$  = 17.2, 10.3, 7.4 Hz), 7.14 (1H, m), 7.27 (2H, d,  $J$  = 5.8 Hz);  $\delta_{\text{H}}$  Minor Diastereomer 0.94 (9H, s), 1.43 (9H, s), 3.73 (3H, s), 4.27 (1H, d,  $J$  = 8.7 Hz), 4.33 (1H, d,  $J$  = 8.7 Hz), 4.76 (1H, d,  $J$  = 10.8 Hz), 4.81 (1H, d,  $J$  = 10.8 Hz), 5.10–5.19 (2H, m), 5.45 (1H, d,  $J$  = 10.3), 5.53 (1H, d,  $J$  = 17.2 Hz), 5.77 (1H, ddd,  $J$  = 17.2, 10.3, 7.4 Hz), 7.14 (1H, m), 7.36 (2H, d,  $J$  = 8.0 Hz); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>, 328K)  $\delta_{\text{C}}$  26.5, 28.3, 38.4, 51.9, 66.1, 70.3, 72.3, 79.3, 80.8, 98.3, 119.9, 128.2, 129.5, 134.0, 134.3, 136.9, 153.2, 170.7; HRMS (ESI, +ve)  $m/z$  calcd. for C<sub>24</sub>H<sub>33</sub>Cl<sub>2</sub>NO<sub>6</sub>Na 524.1583, found: 5224.1571 (M+Na)<sup>+</sup>.

**(2*R*,4*R*)-3-*tert*-Butyl 4-methyl 2-*tert*-butyl-4-((*S*)-1-(2-iodobenzyloxy)allyl) oxazolidine-3,4-dicarboxylate (252m)**



Crude (2*R*,4*S*)-3-*tert*-butyl 4-((*E*)-3-(2-iodobenzyloxy)allyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate **251m** (200 mg, 0.367 mmol), TMSCl (140  $\mu$ L, 1.10 mmol), LHMDS (1M, 1.10 mL, 1.10 mmol) and THF (2.00 mL) were combined according to general procedure VII (reaction time: 18 hours). Purification by flash chromatography (8:1 Pet/EtOAc) affords the methyl ester as a colourless oil (104 mg, 51%, dr >99:1).  $[\alpha]_D^{20} +5.3$  (*c* 3.0, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2978, 2957, 2912, 1743, 1706; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 328K)  $\delta_H$  0.97 (9H, s), 1.35 (9H, s), 3.77 (3H, s), 4.35 (2H, d, *J* = 10.5 Hz), 4.44 (1H, d, *J* = 8.5 Hz), 4.50 (1H, d, *J* = 11.2 Hz), 5.20 (1H, s), 5.25 (1H, bs), 5.36 (1H, d, *J* = 10.3 Hz), 5.42 (1H, d, *J* = 17.2 Hz), 5.80 (1H, ddd, *J* = 17.2, 10.3, 6.9 Hz), 6.95 (1H, t, *J* = 7.7 Hz), 7.36 (1H, t, *J* = 7.7 Hz), 7.52 (1H, d, *J* = 7.7 Hz), 7.76 (1H, d, *J* = 7.7 Hz); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, 328K)  $\delta_C$  26.2, 28.0, 38.3, 52.2, 70.0, 72.4, 74.5, 78.0, 81.0, 95.8, 98.4, 120.1, 127.9, 128.0, 128.5, 133.7, 138.6, 140.8, 153.6, 170.8; HRMS (ESI, +ve) *m/z* calcd. for C<sub>24</sub>H<sub>34</sub>INO<sub>6</sub>Na 582.1329, found: 582.1344 (M+Na)<sup>+</sup>.

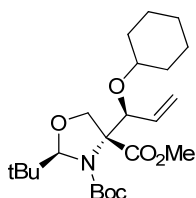
**(2*R*,4*R*)-3-*tert*-Butyl 4-methyl 2-*tert*-butyl-4-((*S*)-1-isobutoxyallyl)oxazolidine-3,4-dicarboxylate (252n)**



Crude (2*R*,4*S*)-3-*tert*-butyl 4-((*E*)-3-isobutoxyallyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate **251n** (154 mg, 0.400 mmol), TMSCl (153  $\mu$ L, 1.20 mmol), LHMDS (1M, 1.2 mL, 1.20 mmol) and THF (1.50 mL) were combined according to general procedure VII (reaction time: 18 hours). Purification by flash chromatography (10:1 Pet/EtOAc) affords the methyl ester as a colourless oil (88 mg, 55%, dr >99:1).  $[\alpha]_D^{20} +8$  (*c* 3.0, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2958, 2909, 2874, 1744, 1712; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 328K)  $\delta_H$  0.88 (3H, d, *J* = 6.7 Hz), 0.90 (3H, d, *J* = 6.7 Hz), 0.95 (9H, s), 1.49 (9H, s), 1.83 (1H, sept., *J* = 6.7 Hz), 3.09 (1H, dd, *J* = 8.2, 6.1 Hz), 3.19 (1H, t, *J* = 8.2 Hz), 3.72 (3H, s), 4.25 (1H, d, *J* = 8.5 Hz), 4.31 (1H, d, *J* = 8.5 Hz), 4.89 (1H, bs), 5.12 (1H, s), 5.29 (1H, d, *J* = 10.5 Hz), 5.34 (1H, d, *J* = 17.3 Hz), 5.72 (1H, ddd, *J* = 17.3, 10.5, 6.8 Hz); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, 328K)  $\delta_C$  19.2, 19.5, 26.3, 28.3, 28.7,

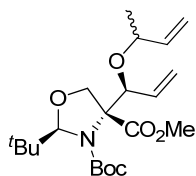
38.4, 51.9, 70.0, 72.3, 75.4, 77.7, 80.6, 98.3, 119.2, 134.8, 153.5, 171.0; HRMS (ESI, +ve)  $m/z$  calcd. for  $C_{21}H_{37}NO_6Na$  422.2519, found: 422.2509 ( $M+Na$ )<sup>+</sup>.

**(2*R*,4*R*)-3-*tert*-Butyl 4-methyl 2-*tert*-butyl-4-((*S*)-1-(cyclohexyloxy)allyl)oxazolidine-3,4-dicarboxylate (252o)**



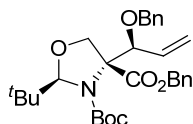
Crude (2*R*,4*S*)-3-*tert*-butyl 4-((*E*)-3-(cyclohexyl)allyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate **252o** (200 mg, 0.486 mmol), TMSCl (186  $\mu$ L, 1.46 mmol), LHMDs (1M, 1.46 mL, 1.46 mmol) and THF (2.00 mL) were combined according to general procedure VII (reaction time: 18 hours). Purification by flash chromatography (15:1 Pet/EtOAc) affords the methyl ester as a colourless oil (97 mg, 47%, dr >99:1).  $[\alpha]_D^{20} +20$  ( $c$  2.0,  $CH_2Cl_2$ ); FTIR (film/ $cm^{-1}$ )  $\nu_{max}$ : 2986, 2936, 2860, 1740, 1703;  $^1H$  NMR (500 MHz,  $CDCl_3$ , 328K)  $\delta_H$  0.98 (9H, s), 1.11–1.35 (5H, m), 1.47–1.53 (10H, s), 1.64–1.76 (2H, m), 1.80–1.93 (2H, m), 3.32–3.40 (1H, m), 3.72 (3H, s), 4.26 (1H, d,  $J$  = 8.4 Hz), 4.31 (1H, d,  $J$  = 8.4 Hz), 5.06 (1H, bs), 5.13 (1H, s), 5.25 (1H, d,  $J$  = 10.6 Hz), 5.39 (1H, d,  $J$  = 17.3 Hz), 5.88 (1H, ddd,  $J$  = 17.3, 10.6, 3.9 Hz);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ , 328K)  $\delta_C$  24.2, 24.3, 25.7, 26.6, 28.3, 32.4, 33.5, 38.7, 51.8, 70.5, 72.3, 80.9, 98.4, 118.6, 136.8, 153.1, 171.0; HRMS (ESI, +ve)  $m/z$  calcd. for  $C_{23}H_{39}NO_6Na$  448.2675, found: 448.2671 ( $M+Na$ )<sup>+</sup>.

**(2*R*,4*R*)-3-*tert*-Butyl 4-methyl 4-((*S*)-1-(but-3-en-2-yloxy)allyl)-2-*tert*-butyloxazolidine-3,4-dicarboxylate (252p)**



(2*R*,4*S*)-4-((*E*)-3-(But-3-en-2-yloxy)allyl) 3-*tert*-butyl 2-*tert*-butyloxazolidine-3,4-dicarboxylate **251p** (200 mg, 0.522 mmol), TMSCl (200  $\mu$ L, 1.56 mmol), LHMDs (1M, 1.56 mL, 1.56 mmol) and THF (2.00 mL) were combined according to general procedure VII (reaction time: 18 hours). Purification by flash chromatography (10:1 Pet/EtOAc) affords the methyl ester as a colourless oil (149 mg, 72%, dr 1:1). FTIR (film/cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 2979, 2912, 2872, 1744, 1714; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>, 328K)  $\delta_{\text{H}}$  Diastereomer A 0.97 (9H, s), 1.20 (3H, d,  $J = 6.4$  Hz), 1.49 (9H, s), 3.71 (3H, s), 4.01 (1H, app. quint.,  $J = 6.4$  Hz), 4.25–4.33 (2H, m), 4.95–5.15 (4H, m), 5.23–5.39 (2H, m), 5.72–5.87 (2H, m);  $\delta_{\text{H}}$  Diastereomer B 0.98 (9H, s), 1.22 (3H, d,  $J = 6.4$  Hz), 1.50 (9H, s), 3.73 (3H, s), 4.01 (1H, app. quint.,  $J = 6.4$  Hz), 4.25–4.33 (2H, m), 4.95–5.15 (4H, m), 5.23–5.39 (2H, m), 5.72–5.87 (2H, m); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>, 328K)  $\delta_{\text{C}}$  Diastereomer A 20.8, 26.5, 28.3, 38.6, 51.8, 70.5, 72.2, 74.4, 75.4, 80.8, 98.3, 114.2, 119.1, 135.3, 140.3, 153.1, 170.9;  $\delta_{\text{C}}$  Diastereomer B 21.6, 26.6, 28.3, 38.7, 51.9, 70.5, 72.3, 74.4, 75.9, 81.0, 98.4, 115.9, 119.8, 136.1, 141.2, 153.2, 171.0; HRMS (ESI, +ve)  $m/z$  calcd. for C<sub>21</sub>H<sub>35</sub>NO<sub>6</sub>Na 420.2362, found: 420.2347 (M+Na)<sup>+</sup>.

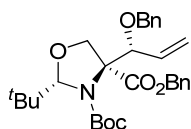
**(2*R*,4*R*)-4-Benzyl 3-*tert*-butyl 4-((*S*)-1-(benzyloxy)allyl)-2-(*tert*-butyl)oxazolidine-3,4-dicarboxylate (254j)**



To a solution of (2*R*,4*S*)-3-*tert*-butyl 4-((*E*)-3-(benzyloxy)allyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate **251j** (200 mg, 0.480 mmol) in THF (2.00 mL) at -78 °C was added TMSCl (183  $\mu$ L, 1.44 mmol). After 10 mins LHMDs (1M, 1.44 mL, 1.44 mmol) was added *via* syringe pump at an addition rate of 0.5 mL min<sup>-1</sup> and reaction mixture allowed to warm to room temperature after a period of 30 mins, and stirred for 18 hours. The reaction was quenched by the addition of 1N HCl and brine solution (1:1, 5 mL) and extracted with DCM (3  $\times$  15 mL), EtOAc (1  $\times$  15 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to afford the crude acid. Residue dissolved in Acetone (5 mL) and K<sub>2</sub>CO<sub>3</sub> (66 mg, 0.48 mmol) and BnBr (143  $\mu$ L, 1.20 mmol) added and allowed to stir for 12 hours. Partitioned between EtOAc (25 mL) and sat. NaHCO<sub>3</sub> (25 mL) and the

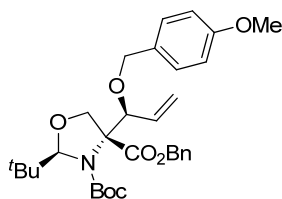
organic layer washed with brine (1 × 25 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to afford the benzyl ester as a colourless oil (175 mg, 72%, dr >99:1). [ $\alpha$ ]<sub>D</sub><sup>20</sup> -9.3 (*c* 3.0, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 2978, 2905, 2875, 1739, 1705; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>, 328K)  $\delta_{\text{H}}$  0.94 (9H, s), 1.40 (9H, s), 4.35 (1H, d, *J* = 8.6 Hz), 4.38–4.47 (2H, m), 4.56 (1H, d, *J* = 11.4 Hz), 5.12–5.27 (4H, m), 5.32 (1H, d, *J* = 10.5 Hz), 5.36 (1H, d, *J* = 17.3 Hz), 5.80 (1H, ddd, *J* = 17.3, 10.5, 6.9 Hz), 7.22–7.29 (1H, m), 7.29–7.39 (7H, m), 7.40–7.45 (2H, m); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>, 328K)  $\delta_{\text{C}}$  26.3, 28.1, 38.4, 67.1, 70.0, 70.6, 72.4, 78.1, 80.9, 98.4, 120.0, 126.9, 127.1, 128.1, 128.2, 128.4, 128.4, 134.1, 135.5, 138.5, 153.7, 170.2; HRMS (ESI, +ve) *m/z* calcd. for C<sub>30</sub>H<sub>40</sub>NO<sub>6</sub> 510.2856, found: 510.2834 (M+H)<sup>+</sup>.

**(2*S*,4*S*)-4-Benzyl 3-*tert*-butyl 4-((*R*)-1-(benzyloxy)allyl)-2-*tert*-butyloxazolidine-3,4-dicarboxylate (*ent*-254j)**



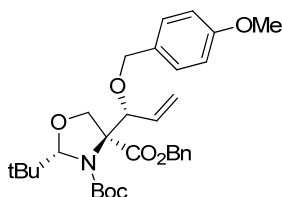
To a solution of (2*S*,4*R*)-3-*tert*-butyl 4-((*E*)-3-(benzyloxy)allyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate *ent*-251j (225 mg, 0.536 mmol) in THF (2.30 mL) at -78 °C was added TMSCl (205  $\mu$ L, 1.61 mmol). After 10 mins LHMDS (1M, 1.61 mL, 1.61 mmol) was added *via* syringe pump at an addition rate of 0.5 mL min<sup>-1</sup> and reaction mixture allowed to warm to room temperature after a period of 30 mins, and stirred for 18 hours. The reaction was quenched by the addition of 1N HCl and brine solution (1:1, 5 mL) and extracted with DCM (3 × 15 mL), EtOAc (1 × 15 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to afford the crude acid. Residue dissolved in Acetone (5 mL) and K<sub>2</sub>CO<sub>3</sub> (74 mg, 0.536 mmol) and BnBr (160  $\mu$ L, 1.34 mmol) added and allowed to stir for 12 hours. Partitioned between EtOAc (25 mL) and sat. NaHCO<sub>3</sub> (25 mL) and the organic layer washed with brine (1 × 25 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to afford the benzyl ester as a colourless oil (164 mg, 60%, dr >99:1). [ $\alpha$ ]<sub>D</sub><sup>20</sup> +9.3 (*c* 2.7, CH<sub>2</sub>Cl<sub>2</sub>). All other data as previously stated.

**(2*R*,4*R*)-4-Benzyl 3-*tert*-butyl 2-*tert*-butyl-4-((*R*)-1-(4-methoxybenzyloxy)allyl)oxazolidine-3,4-dicarboxylate (254k)**



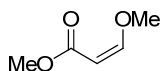
To a solution of (2*R*,4*S*)-3-*tert*-butyl 4-((*E*)-3-(4-methoxybenzyloxy)allyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate **251k** (1.29 g, 2.87 mmol) in THF (13.0 mL) at -78 °C was added TMSCl (1.10 mL, 8.61 mmol). After 10 mins LHMDS (1M, 8.61 mL, 8.61 mmol) was added *via* syringe pump at an addition rate of 0.5 mL min<sup>-1</sup> and reaction mixture allowed to warm to room temperature after a period of 30 mins, and stirred for 18 hours. The reaction was quenched by the addition of 1N HCl and brine solution (1:1, 5 mL) and extracted with DCM (3 × 15 mL), EtOAc (1 × 15 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to afford the crude acid. Residue dissolved in Acetone (15 mL) and K<sub>2</sub>CO<sub>3</sub> (397 mg, 2.87 mmol) and BnBr (854 μL, 7.18 mmol) added and allowed to stir for 3 hours. Partitioned between EtOAc (50 mL) and sat. NaHCO<sub>3</sub> (50 mL) and the organic layer washed with brine (1 × 50 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to afford the benzyl ester as a colourless oil (895 mg, 58%, dr >99:1). [ $\alpha$ ]<sub>D</sub><sup>20</sup> -11.5 (*c* 2.0, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 2977, 2961, 2910, 1737, 1706; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>, 328K)  $\delta_{\text{H}}$  0.94 (9H, s), 1.42 (9H, s), 3.80 (3H, s), 4.32 (1H, d, *J* = 8.6 Hz), 4.35–4.41 (2H, m), 4.48 (1H, d, *J* = 11.0 Hz), 5.12–5.26 (4H, m), 5.31 (1H, d, *J* = 10.5 Hz), 5.36 (1H, d, *J* = 17.3 Hz), 5.74–5.84 (1H, m), 6.87 (2H, app. d, *J* = 8.7 Hz), 7.25 (2H, app. d, *J* = 8.7 Hz), 7.30–7.44 (5H, m); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>, 328K)  $\delta_{\text{C}}$  26.3, 28.2, 38.4, 55.2, 67.1, 70.1, 70.4, 72.4, 78.1, 80.9, 98.4, 113.7, 119.8, 128.2, 128.4, 128.5, 130.0, 130.7, 134.2, 135.5, 153.7, 159.1, 170.2; HRMS (ESI, +ve) *m/z* calcd. for C<sub>31</sub>H<sub>42</sub>NO<sub>7</sub> 540.2961, found: 540.2986 (M+H)<sup>+</sup>.

**(2*S*,4*S*)-4-Benzyl 3-*tert*-butyl 2-*tert*-butyl-4-((*R*)-1-(4-methoxybenzyloxy)allyl) oxazolidine-3,4-dicarboxylate (*ent*-254k)**



To a solution of (2*S*,4*R*)-3-*tert*-butyl 4-((*E*)-3-(4-methoxybenzyloxy)allyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate *ent*-251k (700 mg, 1.56 mmol) in THF (7.0 mL) at -78 °C was added TMSCl (596  $\mu$ L, 4.68 mmol). After 10 mins LHMDS (1M, 4.68 mL, 4.68 mmol) was added *via* syringe pump at an addition rate of 0.5 mL min<sup>-1</sup> and reaction mixture allowed to warm to room temperature after a period of 30 mins, and stirred for 18 hours. The reaction was quenched by the addition of 1N HCl and brine solution (1:1, 5 mL) and extracted with DCM (3  $\times$  15 mL), EtOAc (1  $\times$  15 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to afford the crude acid. Residue dissolved in Acetone (15 mL) and K<sub>2</sub>CO<sub>3</sub> (216 mg, 1.56 mmol) and B5nBr (464  $\mu$ L, 3.90 mmol) added and allowed to stir for 3 hours. Partitioned between EtOAc (50 mL) and sat. NaHCO<sub>3</sub> (50 mL) and the organic layer washed with brine (1  $\times$  50 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to afford the benzyl ester as a colourless oil (500 mg, 60%, dr >99:1). [ $\alpha$ ]<sub>D</sub><sup>20</sup> +10.6 (*c* 2.45, CH<sub>2</sub>Cl<sub>2</sub>). All other data as previously stated.

**(*Z*)-Methyl 3-methoxyacrylate (255)**

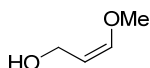


To solution of silver(I) trifluoromethane sulphonate (385 mg, 1.50 mmol, 10 mol%) in methanol (15 mL) was added methyl propiolate (1.33 mL, 15.0 mmol, 1.0 eq). The reaction mixture was stirred at room temperature for 21 hours and concentrated *in vacuo*. The residue was taken up in chloroform (50 mL), filtered through celite and the filtrate concentrated *in vacuo* to afford the pure vinylogous carbonate as a colourless oil (1.62 g, 93%). <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta$ <sub>H</sub> 3.66 (3H, s), 3.86 (3H, s), 4.82 (1H, d, *J*



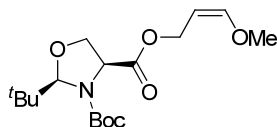
= 7.1 Hz), 6.44 (1H, d,  $J$  = 7.1 Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  51.0, 62.6, 96.0, 160.2, 165.7. All analytical data is in accordance with literature precedence.<sup>297</sup>

**(Z)-3-Methoxyprop-2-en-1-ol (256)**

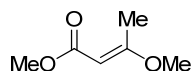


(Z)-Methyl 3-methoxyacrylate **255** (1.62 g, 14.0 mmol) was reduced according to general procedure II (reaction time 4 hours) to afford the product as a pale yellow oil (699 mg, 57%).  $^1\text{H}$  NMR (500MHz,  $\text{d}_6$ -acetone)  $\delta_{\text{H}}$  3.37 (1H, t,  $J$  = 5.6 Hz), 3.57 (3H, s), 4.09 (2H, m), 4.52 (1H, q,  $J$  = 6.6 Hz), 5.96 (1H, dt,  $J$  = 6.6, 1.3 Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{d}_6$ -acetone)  $\delta_{\text{C}}$  55.7, 59.8, 107.5, 147.7. All analytical data is in accordance with literature precedence.<sup>298</sup>

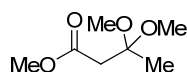
**(2R,4S)-3-tert-Butyl 4-((Z)-3-methoxyallyl) 2-tert-butyloxazolidine-3,4-dicarboxylate (257)**



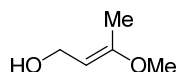
EDCI.HCl (767 mg, 4.00 mmol), triethylamine (560  $\mu\text{L}$ , 4.00 mmol), (2R,4S)-3-(tert-butoxycarbonyl)-2-tert-butyloxazolidine-4-carboxylic acid **250** (1.09 g, 4.00 mmol), DMAP (5 mol%), DCM (100 mL) and (Z)-3-methoxyprop-2-en-1-ol **256** (176 mg, 2.00 mmol) were combined according to general procedure IV (reaction time: 2 hours). Purified on a short pad of silica (2:1 Pet:EtOAc + 1%  $\text{Net}_3$ ) to afford the title compound as a colourless oil (330 mg, 48%).  $[\alpha]_{\text{D}}^{20}$  -19.6 ( $c$  2.3,  $\text{CHCl}_3$ ); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2974, 2939, 2909, 2872, 1734, 1705, 1665;  $^1\text{H}$  NMR (500MHz,  $\text{d}_6$ -acetone)  $\delta_{\text{H}}$  0.93 (9H, s), 1.46 (9H, s), 3.66 (3H, s), 4.14–4.22 (2H, m), 4.51–4.61 (2H, m), 4.67 (1H, app d,  $J$  = 7.2 Hz), 4.71 (1H, t,  $J$  = 7.2 Hz), 4.99 (1H, s), 6.23 (1H, d,  $J$  = 6.1 Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{d}_6$ -acetone)  $\delta_{\text{C}}$  25.4, 27.5, 37.5, 57.3, 58.3, 59.8, 68.2, 80.3, 97.2, 99.4, 150.8, 154.8, 170.2; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{17}\text{H}_{30}\text{NO}_6$  344.2073, found: 344.2056 ( $\text{M}+\text{H}$ ) $^+$ .

**(E)-Methyl 3-methoxybut-2-enoate (259)**

To a stirred solution of methyl acetoacetate (4.00 mL, 37.0 mmol, 1.0 eq) and trimethyl orthoformate (4.12 mL, 37.6 mmol, 1.02 eq) at room temperature was added 3 drops of conc. H<sub>2</sub>SO<sub>4</sub> and reaction mixture stirred at room temperature for 24 hours. Partitioned between NaHCO<sub>3</sub> (sat) (50 mL) and DCM and extracted with DCM (3 × 50 mL). The organics were combined, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. Purified by flash chromatography (20:1 Pet/EtOAc) to afford the pure vinylogous carbonate as a colourless liquid (2.87 g, 60%). <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 2.30 (3H, s), 3.63 (3H, s), 3.68 (3H, s), 5.03 (1H, s); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>) δ<sub>C</sub> 18.9, 50.8, 55.4, 90.5, 168.4, 173.3. All analytical data is in accordance with literature precedence.<sup>206</sup>

**Methyl 3,3-dimethoxybutanoate (260)**

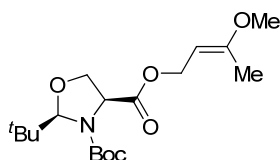
Undesired side product from synthesis of (*E*)-methyl 3-methoxybut-2-enoate **259**. <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 1.47 (3H, s), 2.69 (2H, s), 3.23 (6H, s), 3.70 (3H, s); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>) δ<sub>C</sub> 21.8, 42.1, 48.4, 51.8, 99.8, 170.2. All analytical data is in accordance with literature precedence.<sup>299</sup>

**(E)-3-Methoxybut-2-en-1-ol (261)**

(*E*)-Methyl 3-methoxybut-2-enoate **259** (780 mg, 6 mmol) was reduced according to general procedure II (reaction time 4 hours) to afford the product as a colourless oil (484 mg, 79%). <sup>1</sup>H NMR (500MHz, d<sub>6</sub>-acetone) δ<sub>H</sub> 1.77 (3H, s), 3.26 (1H, t, *J* = 5.6 Hz), 3.47 (3H, s), 4.04 (2H, dd, *J* = 7.4, 5.6 Hz), 4.67 (1H, t, *J* = 7.4 Hz); <sup>13</sup>C NMR

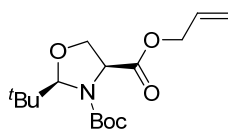
(125MHz,  $d_6$ -acetone)  $\delta_C$  16.3, 54.3, 58.8, 97.8, 157.0. All analytical data is in accordance with literature precedence.<sup>300</sup>

**(2*R*,4*S*)-3-*tert*-Butyl 4-((*E*)-3-methoxybut-2-enyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate (262)**



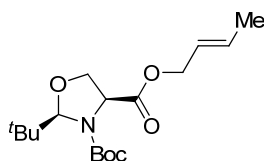
EDCi.HCl (767 mg, 4.00 mmol), triethylamine (560  $\mu$ L, 4.00 mmol), (2*R*,4*S*)-3-(*tert*-butoxycarbonyl)-2-*tert*-butyloxazolidine-4-carboxylic acid **250** (1.09 g, 4.00 mmol), DMAP (5 mol%), DCM (100 mL) and (*E*)-3-methoxybut-2-en-1-ol **261** (204 mg, 2.00 mmol) were combined according to general procedure IV (reaction time: 3 hours) to afford the title compound as a pale yellow oil (quant) which used in its crude form.

**(2*R*,4*S*)-4-Allyl 3-*tert*-butyl 2-*tert*-butyloxazolidine-3,4-dicarboxylate (265a)**



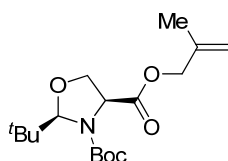
Allyl alcohol (58  $\mu$ L, 0.85 mmol), (2*R*,4*S*)-3-(*tert*-butoxycarbonyl)-2-*tert*-butyloxazolidine-4-carboxylic acid **250** (255 mg, 0.94 mmol), EDCi.HCl (180 mg, 0.94 mmol), triethylamine (131  $\mu$ L, 0.94 mmol), DMAP (5 mol%) and DCM (40 mL) were combined according to general procedure II to afford the title compound as a yellow oil (224 mg, 84%).  $[\alpha]_D^{20}$  -19.5 ( $c$  1.2,  $CH_2Cl_2$ ); FTIR (film/ $cm^{-1}$ )  $\nu_{max}$ : 2975, 2906, 2871, 1759, 1704, 1480;  $^1H$  NMR (500MHz,  $CDCl_3$ )  $\delta_H$  0.94 (9H, s), 1.46 (9H, s), 4.18 (1H, t,  $J$  = 8.6 Hz), 4.26 (1H, dd,  $J$  = 8.6, 6.5 Hz), 4.64 (2H, qd,  $J$  = 13.4, 5.7 Hz), 4.70 (1H, bs), 5.04 (1H, s), 5.24 (1H, d,  $J$  = 10.5 Hz), 5.34 (1H, dd,  $J$  = 17.2, 1.3 Hz), 5.85-5.95 (1H, m);  $^{13}C$  NMR (125MHz,  $CDCl_3$ )  $\delta_C$  25.8, 28.2, 37.8, 59.7, 65.8, 68.4, 81.3, 97.6, 118.6, 131.6, 155.0, 170.1; HRMS (ESI, +ve)  $m/z$  calcd. for  $C_{16}H_{27}NO_5Na$  336.1787, found: 336.1780 ( $M+Na$ )<sup>+</sup>.

**(2*R*,4*S*)-4-((*E*)-But-2-enyl) 3-*tert*-butyl 2-*tert*-butyloxazolidine-3,4-dicarboxylate (265b)**



Crotyl alcohol (156  $\mu$ L, 1.83 mmol), (2*R*,4*S*)-3-(*tert*-butoxycarbonyl)-2-*tert*-butyloxazolidine-4-carboxylic acid **250** (550 mg, 2.01 mmol), EDCi.HCl (386 mg, 2.01 mmol), triethylamine (282  $\mu$ L, 2.01 mmol), DMAP (5 mol%) and DCM (90 mL) were combined according to general procedure II to afford the title compound as a pale yellow oil (157 mg, 84%).  $[\alpha]_{\text{D}}^{20}$  -23.6 (*c* 1.1, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 2963, 2912, 1758, 1706, 1479; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  0.94 (9H, s), 1.46 (9H, s), 1.71 (3H, d, *J* = 6.6 Hz), 4.17 (1H, t, *J* = 8.5 Hz), 4.24 (1H, t, *J* = 8.5 Hz), 4.57 (2H, d, *J* = 6.5 Hz), 4.67 (1H, bs), 5.04 (1H, s), 5.58 (1H, dtd, *J* = 15.3, 6.6, 1.6 Hz), 5.81 (1H, dq, *J* = 15.3, 6.6 Hz); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  17.7, 25.8, 28.2, 37.9, 59.8, 65.9, 68.5, 81.2, 97.6, 124.6, 131.8, 155.0, 170.2; HRMS (ESI, +ve) *m/z* calcd. for C<sub>17</sub>H<sub>29</sub>NO<sub>5</sub>Na 350.1943, found: 350.1935 (M+Na)<sup>+</sup>.

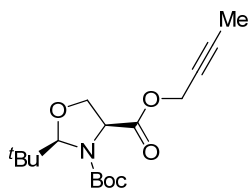
**(2*R*,4*S*)-3-*tert*-Butyl 4-(2-methylallyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate (265c)**



2-Methyl-2-propen-1-ol (154  $\mu$ L, 1.83 mmol), (2*R*,4*S*)-3-(*tert*-butoxycarbonyl)-2-*tert*-butyloxazolidine-4-carboxylic acid **250** (550 mg, 2.01 mmol), EDCi.HCl (386 mg, 2.01 mmol), triethylamine (282  $\mu$ L, 2.01 mmol), DMAP (5 mol%) and DCM (90 mL) were combined according to general procedure II to afford the title compound as a yellow oil (250 mg, 97%).  $[\alpha]_{\text{D}}^{20}$  -20.8 (*c* 1.3, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 2976, 1760, 1709, 1480; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  0.94 (9H, s), 1.47 (9H, s), 1.76 (3H, s), 4.17 (1H, t, *J* = 8.6 Hz), 4.28 (1H, dd, *J* = 8.6, 6.2 Hz), 4.50 (1H, d, *J* = 13.1 Hz), 4.61 (1H, d, *J* =

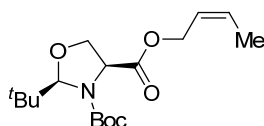
13.1 Hz), 4.73 (1H, bs), 4.94 (1H, s), 5.01 (1H, s), 5.05 (1H, s);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  19.4, 25.8, 28.2, 37.8, 59.7, 68.4, 68.5, 81.3, 97.6, 113.4, 139.3, 155.0, 170.1; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{17}\text{H}_{29}\text{NO}_5\text{Na}$  350.1943, found: 350.1932 ( $\text{M}+\text{Na}$ ) $^{+}$ .

**(2*R*,4*S*)-4-But-2-ynyl 3-*tert*-butyl 2-*tert*-butyloxazolidine-3,4-dicarboxylate (265d)**



2-Butyn-1-ol (233 mg, 3.33 mmol), (2*R*,4*S*)-3-(*tert*-butoxycarbonyl)-2-*tert*-butyloxazolidine-4-carboxylic acid **250** (1.00 g, 3.66 mmol), EDCi.HCl (638 mg, 3.33 mmol), triethylamine (463  $\mu\text{L}$ , 3.33 mmol), DMAP (5 mol%) and DCM (100 mL) were combined according to general procedure II to afford the title compound as a yellow oil (779 mg, 72%).  $[\alpha]_{\text{D}}^{20}$  -19.3 ( $c$  1.4,  $\text{CH}_2\text{Cl}_2$ ); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2973, 2874, 1764, 1742, 1707, 1480;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  0.96 (9H, s), 1.48 (9H, s), 1.84 (3H, t,  $J$  = 2.4 Hz), 4.20 (1H, t,  $J$  = 8.6 Hz), 4.27 (1H, t,  $J$  = 8.6 Hz), 4.72 (3H, app. q,  $J$  = 2.4 Hz), 5.05 (1H, s);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  3.6, 25.8, 28.2, 37.9, 53.5, 59.6, 68.4, 72.7, 81.3, 83.6, 97.7, 155.0, 170.0; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{17}\text{H}_{27}\text{NO}_5\text{Na}$  348.1787, found: 348.1768 ( $\text{M}+\text{Na}$ ) $^{+}$ .

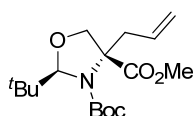
**(2*R*,4*S*)-4-((*Z*)-But-2-en-1-yl) 3-*tert*-butyl 2-(*tert*-butyl)oxazolidine-3,4-dicarboxylate (265e)**



To a solution of (2*R*,4*S*)-4-But-2-ynyl 3-*tert*-butyl 2-*tert*-butyloxazolidine-3,4-dicarboxylate **265d** (300 mg, 0.92 mmol) in EtOAc (22 mL) was added Lindlar catalyst (5 mol%) and quinoline (5 mol%) and the reaction was stirred at room temperature under an atmosphere of hydrogen for 90 min. The reaction mixture was filtered through

celite and the filtrate concentrated *in vacuo*. Purification by flash chromatography (4:1 Pet:EtOAc) afforded the title compound as a pale yellow oil (172 mg, 57%).  $[\alpha]_D^{20}$  -27.5 (*c* 1.2, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2975, 2939, 2909, 2875, 1759, 1706, 1479; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_H$  0.93 (9H, s), 1.45 (9H, s), 1.69 (3H, dd, *J* = 7.0, 0.8 Hz), 4.20 (1H, t, *J* = 8.5 Hz), 4.27 (1H, dd, *J* = 8.5, 6.2 Hz), 4.66 (1H, bs), 4.70 (2H, d, *J* = 7.0 Hz), 5.03 (1H, s), 5.36-5.44 (1H, m), 5.68-5.76 (1H, m); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_C$  13.1, 25.8, 28.2, 37.8, 59.7, 60.8, 68.5, 81.2, 97.6, 123.7, 130.1, 155.0, 170.3; HRMS (ESI, +ve) *m/z* calcd. for C<sub>17</sub>H<sub>29</sub>NO<sub>5</sub>Na 350.1943, found: 350.1936 (M+Na)<sup>+</sup>.

**(2*R*,4*S*)-3-*tert*-Butyl 4-methyl 4-allyl-2-*tert*-butyloxazolidine-3,4-dicarboxylate (266a)**



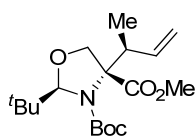
Synthesis *via* Ireland-Claisen Rearrangement (Section 3.4.2 Substrate Rearrangement): (2*R*,4*S*)-4-Allyl 3-*tert*-butyl 2-*tert*-butyloxazolidine-3,4-dicarboxylate **265a** (295 mg, 0.941 mmol), TMSCl (360  $\mu$ L, 2.82 mmol), LiHMDS (1M, 2.82 mL, 2.82 mmol) and THF (3.00 mL) were combined according to general procedure VII (reaction time: 18 hours). Purification by flash chromatography (15:1 Pet/EtOAc) affords the methyl ester as a pale yellow oil (176 mg, 57%).

Synthesis *via* Alkylation (Section 5.2.3 Ligand Development):

To a solution of (2*R*,4*S*)-3-*tert*-butyl 4-methyl 2-*tert*-butyloxazolidine-3,4-dicarboxylate **249** (1.44 g, 5 mmol, 1 eq) and allyl bromide (4.33 mL, 50 mmol, 10 eq) in THF (15 mL) at -84 °C was added LHMDS (1M in THF, 15 mL, 15 mmol, 3 eq) *via* syringe pump at a rate of 10 mL/hr and allowed to stir at -84 °C for 16 hours. Quenched with NH<sub>4</sub>Cl (sat.) (30 mL), diluted with water (30 mL) and extracted with EtOAc (1  $\times$  50 mL) and DCM (2  $\times$  50 mL). The organics were combined, dried over MgSO<sub>4</sub> and concentrated *in vacuo*. Purification by flash chromatography affords the title compound as a colourless oil (1.33 g, 81%).

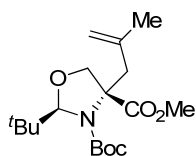
$[\alpha]_D^{20} +11.7$  ( $c$  1.2,  $\text{CH}_2\text{Cl}_2$ ); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2978, 2905, 1742, 1711, 1641, 1478;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  0.97 (9H, s), 1.42 (9H, s), 2.68 (1H, dd,  $J = 14.2$ , 5.8 Hz), 3.08 (1H, s), 3.74 (3H, s), 4.05 (1H, d,  $J = 8.5$  Hz), 4.22 (1H, dd,  $J = 8.5$ , 1.6 Hz), 5.04 (1H, s), 5.08-5.18 (2H, m), 5.75-5.85 (1H, m);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  26.5, 28.1, 39.3, 39.4, 52.4, 68.6, 75.2, 80.8, 98.0, 119.5, 132.0, 153.1, 172.1; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{17}\text{H}_{29}\text{NO}_5\text{Na}$  350.1943, found: 350.1937 ( $\text{M}+\text{Na}$ ) $^+$ .

**(2*R*,4*S*)-3-*tert*-Butyl 4-methyl 4-((*S*)-but-3-en-2-yl)-2-*tert*-butyloxazolidine-3,4-dicarboxylate (266b)**



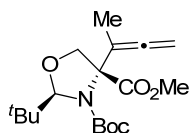
(2*R*,4*S*)-4-((*E*)-But-2-enyl) 3-*tert*-butyl 2-*tert*-butyloxazolidine-3,4-dicarboxylate **265b** (327 mg, 1.00 mmol),  $\text{TMSCl}$  (382  $\mu\text{L}$ , 3.00 mmol),  $\text{LiHMDS}$  (1M, 3.00 mL, 3.00 mmol) and THF (3.30 mL) were combined according to general procedure VII to afford the title compound as a colourless oil (149 mg, 44%).  $[\alpha]_D^{20} -7.5$  ( $c$  1.2,  $\text{CH}_2\text{Cl}_2$ ); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2981, 2953, 2910, 1744, 1709, 1639, 1565, 1478;  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  1.01 (9H, s), 1.05 (3H, d,  $J = 7.0$  Hz), 1.51 (9H, s), 3.71 (1H, s), 3.78 (3H, s), 4.16 (1H, d,  $J = 8.9$  Hz), 4.33 (1H, d,  $J = 8.9$  Hz), 5.15-5.21 (3H, m), 5.94-6.04 (1H, m);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  13.0, 26.5, 28.2, 39.2, 52.2, 60.4, 71.3, 71.6, 81.0, 98.2, 116.4, 139.5, 153.5, 172.1; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{18}\text{H}_{31}\text{NO}_5\text{Na}$  364.2100, found: 364.2066 ( $\text{M}+\text{Na}$ ) $^+$ .

**(2*R*,4*S*)-3-*tert*-Butyl 4-methyl 2-*tert*-butyl-4-(2-methylallyl)oxazolidine-3,4-dicarboxylate (266c)**



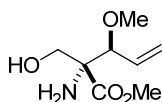
(2*R*,4*S*)-3-*tert*-Butyl 4-(2-methylallyl) 2-*tert*-butyloxazolidine-3,4-dicarboxylate **265c** (160 mg, 0.49 mmol), TMSCl (187  $\mu$ L, 1.47 mmol), LiHMDS (1M, 1.47 mL, 1.47 mmol) and THF (1.2 mL) were combined according to general procedure VII to afford the title compound as a colourless oil (43 mg, 26%).  $[\alpha]_D^{20} +14.5$  (*c* 1.1, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2986, 2956, 2907, 2871, 1743, 1709, 1643, 1478; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_H$  1.02 (9H, s), 1.47 (9H, s), 1.81 (3H, s), 2.69 (1H, d, *J* = 14.1 Hz), 3.13 (1H, bs), 3.77 (3H, s), 4.16 (1H, d, *J* = 8.6 Hz), 4.22 (1H, dd, *J* = 8.6, 1.2 Hz), 4.81 (1H, s), 4.96 (1H, s), 5.08 (1H, s); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_C$  23.6, 26.8, 28.2, 39.5, 40.9, 52.4, 68.9, 74.0, 80.9, 97.9, 116.4, 140.8, 153.0, 172.5; HRMS (ESI, +ve) *m/z* calcd. for C<sub>18</sub>H<sub>31</sub>NO<sub>5</sub>Na 364.2100, found: 364.2095 (M+Na)<sup>+</sup>.

**(2*R*,4*S*)-3-*tert*-Butyl 4-methyl 4-(buta-2,3-dien-2-yl)-2-*tert*-butyloxazolidine-3,4-dicarboxylate (266d)**



(2*R*,4*S*)-4-But-2-ynyl 3-*tert*-butyl 2-*tert*-butyloxazolidine-3,4-dicarboxylate **265d** (200 mg, 0.62 mmol), TMSCl (235  $\mu$ L, 1.85 mmol), LiHMDS (1M, 1.85 mL, 1.85 mmol) and THF (2.00 mL) were combined according to general procedure VII to afford the title compound as colourless crystals (117 mg, 56%).  $[\alpha]_D^{20} -54.5$  (*c* 1.1, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2977, 2910, 2871, 1964, 1763, 1737, 1700, 1479; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_H$  0.95 (s, 9H), 1.45 (s, 9H), 1.72 (3H, t, *J* = 3.1 Hz), 3.72 (3H, s), 4.16 (1H, d, *J* = 9.2 Hz), 4.48 (1H, d, *J* = 9.2 Hz), 4.71-4.81 (2H, m), 5.23 (1H, s); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_C$  14.3, 26.2, 27.9, 39.1, 51.9, 71.7, 75.7, 77.2, 80.4, 98.4, 99.8, 153.5, 170.3, 206.4; HRMS (ESI, +ve) *m/z* calcd. for C<sub>18</sub>H<sub>29</sub>NO<sub>5</sub>Na 362.1943, found: 362.1925 (M+Na)<sup>+</sup>. X-Ray Crystal structure obtained.

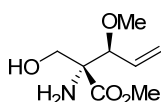
**(±)-(syn)-Methyl 2-amino-2-(hydroxymethyl)-3-methoxypent-4-enoate (*rac*-267)**





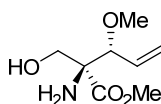
(±)-(anti)-3-*tert*-Butyl 4-methyl 2-*tert*-butyl-4-(1-methoxyallyl)oxazolidine-3,4-dicarboxylate **rac-252a** (65 mg, 0.181 mmol), MeOH (1 mL) and 6N HCl (0.6 mL, 3.62 mmol) were combined according to general procedure IX. Purified by flash chromatography (95:5 DCM:MeOH) to afford the title compound as a colourless oil (16.1 mg, 47%). FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 3365, 3310, 2951, 2897, 2826; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  2.24 (3H, s), 3.24 (3H, s), 3.50 (1H, d,  $J = 10.9$  Hz), 3.76 (1H, d,  $J = 10.9$  Hz), 3.79 (3H, s), 3.87 (1H, d,  $J = 7.9$  Hz), 5.35 (1H, ddd,  $J = 17.3, 1.4, 0.9$  Hz), 5.42 (1H, dd,  $J = 10.3, 1.4$  Hz), 5.71–5.81 (1H, m); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  52.6, 56.7, 65.5, 66.1, 84.7, 121.0, 132.9, 174.6; HRMS (ESI, +ve)  $m/z$  calcd. for C<sub>8</sub>H<sub>15</sub>NO<sub>4</sub>Na 212.0899, found: 212.0881 (M+Na)<sup>+</sup>.

**(2R,3S)-Methyl 2-amino-2-(hydroxymethyl)-3-methoxypent-4-enoate (267)**



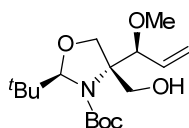
(2*R*,4*R*)-3-*tert*-Butyl 4-methyl 2-*tert*-butyl-4-((*S*)-1-methoxyallyl)oxazolidine-3,4-dicarboxylate **252a** (100 mg, 0.291 mmol), MeOH (2 mL) and 6N HCl (970  $\mu$ L, 5.82 mmol) were combined according to general procedure IX (reaction time: 8 hours) to afford the title compound as a colourless oil (42 mg, 76%).  $[\alpha]_{\text{D}}^{20}$  -31.3 ( $c$  1.5, CH<sub>2</sub>Cl<sub>2</sub>). All other data as previously stated.

**(2S,3R)-Methyl 2-amino-2-(hydroxymethyl)-3-methoxypent-4-enoate (*ent*-267)**



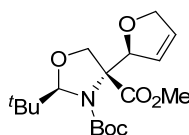
(2*S*,4*S*)-3-*tert*-Butyl 4-methyl 2-*tert*-butyl-4-((*R*)-1-methoxyallyl)oxazolidine-3,4-dicarboxylate **ent-252a** (100 mg, 0.291 mmol), MeOH (2 mL) and 6N HCl (970  $\mu$ L, 5.82 mmol) were combined according to general procedure IX (reaction time: 8 hours) to afford the title compound as a colourless oil (43 mg, 78%).  $[\alpha]_{\text{D}}^{20}$  +31.6 ( $c$  1.9, CH<sub>2</sub>Cl<sub>2</sub>). All other data as previously stated.

**(2*R*,4*R*)-*tert*-Butyl 2-*tert*-butyl-4-(hydroxymethyl)-4-((*S*)-1-methoxyallyl)oxazolidine-3-carboxylate (268)**



To a stirred solution of lithium aluminium hydride in THF (1M, 840  $\mu$ L, 0.840 mmol, 2.0 eq) at 0  $^{\circ}$ C was added a solution of (2*R*,4*R*)-3-*tert*-butyl 4-methyl 2-*tert*-butyl-4-((*S*)-1-methoxyallyl)oxazolidine-3,4-dicarboxylate **252a** (150 mg, 0.420 mmol, 1.0 eq) in THF (4 mL) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 4 hours. Reaction mixture poured into an ice-cold solution of saturated Rochelle salt (15 mL) and EtOAc (10 mL). The biphasic mixture was stirred vigorously at room temperature for 2 hours before extracting with EtOAc (3  $\times$  25 mL). The organics were combined, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to afford the pure title compound without the need for further purification as a colourless oil (138 mg, 100%).  $[\alpha]_D^{20}$  +24.6 (*c* 1.26, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 3390, 2978, 2935, 2825, 1694, 1664; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_H$  0.97 (9H, s), 1.53 (9H, s), 3.30 (3H, s), 3.47 (1H, d, *J* = 8.7 Hz), 3.53 (1H, d, *J* = 11.7 Hz), 3.79 (1H, d, *J* = 11.7 Hz), 4.20 (1H, d, *J* = 8.7 Hz), 4.69 (1H, bs), 5.14 (1H, s), 5.40 (1H, d, *J* = 10.5 Hz), 5.50 (1H, d, *J* = 17.4 Hz), 5.71–5.81 (1H, m); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_C$  26.6, 28.2, 38.6, 57.2, 65.9, 69.5, 70.8, 78.9, 82.0, 98.5, 119.5, 134.2, 156.4; HRMS (ESI, +ve) *m/z* calcd. for C<sub>17</sub>H<sub>31</sub>NO<sub>5</sub>Na 352.2100, found: 352.2104 (M+Na)<sup>+</sup>.

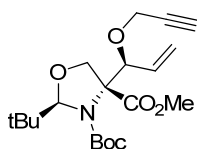
**(2*R*,4*R*)-3-*tert*-Butyl 4-methyl 2-*tert*-butyl-4-((*S*)-2,5-dihydrofuran-2-yl)oxazolidine-3,4-dicarboxylate (270)**



To a solution of (2*R*,4*R*)-3-*tert*-butyl 4-methyl 2-*tert*-butyl-4-((*S*)-1-(allyloxy)allyl)oxazolidine-3,4-dicarboxylate **252d** (69 mg, 0.180 mmol, 1.0 eq) in DCM (500  $\mu$ L) was added Hoveyda-Grubbs II (5 mol%, 6 mg, 0.009 mmol) and stirred

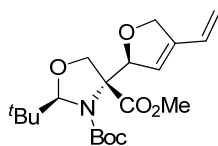
at room temperature for 24 hours. Reaction mixture concentrated *in vacuo* and the residue purified by column chromatography (15:1 Pet/EtOAc) to afford the title compound as a colourless oil (47 mg, 73%).  $[\alpha]_D^{20} +4.0$  (*c* 1.0, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2978, 2957, 2908, 1709; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_H$  0.99 (9H, s), 1.46 (9H, s), 3.78 (3H, s), 4.07 (2H, s), 4.59 (1H, d, *J* = 13.1 Hz), 4.67 (1H, dd, *J* = 13.1, 6.2 Hz), 5.14 (1H, s), 5.66 (1H, bs), 5.97 (1H, d, *J* = 5.9 Hz), 6.08 (1H, d, *J* = 5.9 Hz); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_C$  26.4, 28.2, 39.0, 52.4, 71.2, 71.7, 75.7, 80.8, 85.9, 98.2, 127.8, 129.5, 153.9, 171.7; HRMS (ESI, +ve) *m/z* calcd. for C<sub>18</sub>H<sub>29</sub>NO<sub>6</sub>Na 378.1893, found: 378.1883 (M+Na)<sup>+</sup>.

**(2*R*,4*R*)-3-*tert*-Butyl 4-methyl 2-*tert*-butyl-4-((*S*)-1-(prop-2-ynyloxy)allyl)oxazolidine-3,4-dicarboxylate (272)**



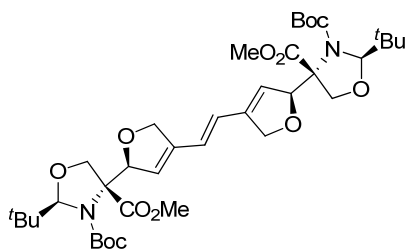
To a solution of (2*R*,4*R*)-3-*tert*-butyl 4-methyl 2-*tert*-butyl-4-((*S*)-1-(prop-2-ynyloxy)allyl)oxazolidine-3,4-dicarboxylate **252e** (474 mg, 1.04 mmol, 1.0 eq) in MeOH (10 mL) was added K<sub>2</sub>CO<sub>3</sub> (360 mg, 2.61 mmol, 2.5 eq) and stirred at room temperature for 30 minutes. Reaction mixture filtered and partitioned between brine and DCM, and extracted with DCM (3 × 15 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to afford the terminal alkyne as a pale yellow oil (359 mg, 91%).  $[\alpha]_D^{20} -3.0$  (*c* 2.0, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 3259, 2979, 2960, 2908, 2872, 1743, 1704; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_H$  0.94 (9H, s), 1.52 (9H, s), 2.37 (1H, t, *J* = 2.4 Hz), 3.73 (3H, s), 4.06 (1H, dd, *J* = 15.0, 2.4 Hz), 4.13 (1H, dd, *J* = 15.0, 2.4 Hz), 4.20 (1H, d, *J* = 8.5 Hz), 4.36 (1H, d, *J* = 8.5 Hz), 5.05 (1H, d, *J* = 7.0 Hz), 5.14 (1H, s), 5.36 (1H, d, *J* = 10.4 Hz), 5.42 (1H, d, *J* = 17.2 Hz), 5.71 (1H, ddd, *J* = 17.2, 10.4, 7.0 Hz); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_C$  26.2, 28.2, 38.2, 52.1, 56.4, 69.8, 72.2, 74.2, 77.8, 79.7, 81.0, 98.2, 120.8, 133.3, 153.6, 170.7; HRMS (ESI, +ve) *m/z* calcd. for C<sub>20</sub>H<sub>31</sub>NO<sub>6</sub>Na 404.2049, found: 404.2044 (M+Na)<sup>+</sup>.

**(2*R*,4*R*)-3-*tert*-Butyl 4-methyl 2-*tert*-butyl-4-((*S*)-4-vinyl-2,5-dihydrofuran-2-yl)oxazolidine-3,4-dicarboxylate (273)**



To a solution of (2*R*,4*R*)-3-*tert*-butyl 4-methyl 2-*tert*-butyl-4-((*S*)-1-(prop-2-ynyloxy)allyl)oxazolidine-3,4-dicarboxylate (40 mg, 0.105 mmol, 1 eq) in DCM (1.75 mL, [0.06M]) under 1 bar ethylene was added Hoveyda-Grubbs II (3.3 mg, 5.24  $\mu$ mol, 5 mol%) and the resulting solution allowed to stir for 24 hours. Reaction mixture concentrated *in vacuo* and purified by flash chromatography (10:1 Pet/EtOAc) to afford the title compound **8** as a colourless oil (20 mg, 50%).  $[\alpha]_D^{20} +36.5$  (*c* 2.3, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm-1)  $\nu_{\max}$ : 2976, 2963, 2936, 2905, 2875, 1717; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_H$  1.02 (9H, s), 1.48 (9H, s), 3.78 (3H, s), 4.04–4.11 (2H, m), 4.66–4.73 (1H, m), 4.79–4.86 (1H, m), 5.05 (1H, d, *J* = 17.7 Hz), 5.18 (1H, s), 5.21 (1H, d, *J* = 10.8 Hz), 5.75 (1H, bs), 5.95 (1H, s), 6.53 (1H, dd, *J* = 17.7, 10.8 Hz); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_C$  26.4, 28.2, 38.9, 52.1, 71.4, 72.1, 74.2, 80.8, 86.0, 98.4, 116.9, 126.2, 129.2, 141.4, 153.8, 171.5; HRMS (ESI, +ve) *m/z* calcd. for C<sub>20</sub>H<sub>31</sub>NO<sub>6</sub>Na 404.2049, found: 404.2038 (M+Na)<sup>+</sup>.

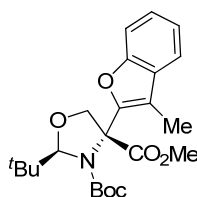
**(2*R*,2'*R*,4*R*,4'*R*)-3-*tert*-Butyl 4-dimethyl 4,4'-((2*S*,2'*S*)-4,4'-((*E*)-ethene-1,2-diyl)bis(2,5-dihydrofuran-4,2-diyl))bis(2-*tert*-butyloxazolidine-3,4-dicarboxylate) (274)**



Unwanted side product from synthesis of (2*R*,4*R*)-3-*tert*-butyl 4-methyl 2-*tert*-butyl-4-((*S*)-4-vinyl-2,5-dihydrofuran-2-yl)oxazolidine-3,4-dicarboxylate **273** (20 mg, 50%).  $[\alpha]_D^{20} +72.0$  (*c* 2, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm-1)  $\nu_{\max}$ : 2976, 2960, 2912, 2875, 1713; <sup>1</sup>H

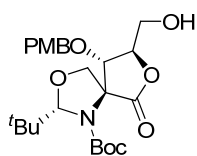
NMR (500MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  1.01 (18H, s), 1.47 (18H, s), 3.79 (6H, s), 4.00–4.10 (4H, m), 4.71 (2H, app. dt,  $J = 11.9, 2.1$  Hz), 4.83 (2H, app. ddd,  $J = 11.9, 5.6, 2.1$  Hz), 5.16 (2H, s), 5.74 (2H, bs), 6.02 (2H, s), 6.17 (2H, s); HRMS (ESI, +ve)  $m/z$  calcd. for C<sub>38</sub>H<sub>58</sub>N<sub>2</sub>O<sub>12</sub>Na 757.3887, found: 757.3874 (M+Na)<sup>+</sup>.

**(2*R*,4*R*)-3-*tert*-Butyl 4-methyl 2-*tert*-butyl-4-(3-methylbenzofuran-2-yl)oxazolidine-3,4-dicarboxylate (275)**



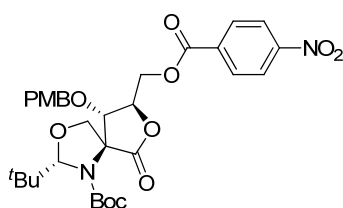
To a solution of palladium(II) acetate (0.6 mg, 2.66  $\mu\text{mol}$ ), triphenylphosphine (0.7 mg, 2.66  $\mu\text{mol}$ ), and silver carbonate (22 mg, 79.8  $\mu\text{mol}$ ) in MeCN was added (2*R*,4*R*)-3-*tert*-butyl 4-methyl 2-*tert*-butyl-4-((*S*)-1-(2-iodophenoxy)allyl)oxazolidine-3,4-dicarboxylate **252i** (29 mg, 53.2  $\mu\text{mol}$ ) and reaction stirred for 18 hours. Concentrated *in vacuo* and purified by flash chromatography (10:1 Pet/EtOAc) to afford a mixture of 5-endo and 5-exo products. Upon standing in CDCl<sub>3</sub> a single isomer of the 5-endo is obtained as a colourless oil (22 mg, 100%).  $[\alpha]_{\text{D}}^{20} -1.8$  ( $c$  1.1, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 2976, 2957, 2909, 2875, 1766, 1741, 1704; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  1.02 (9H, s), 1.11 (9H, s), 2.18 (3H, s), 3.92 (3H, s), 4.48 (1H, d,  $J = 8.9$  Hz), 4.74 (1H, d,  $J = 8.9$  Hz), 5.49 (1H, s), 7.21–7.30 (2H, m), 7.39 (1H, app. d,  $J = 8.2$  Hz), 7.48 (1H, app. d,  $J = 7.5$  Hz); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  7.8, 26.2, 27.6, 38.8, 52.8, 68.7, 76.9, 80.4, 98.7, 111.0, 112.0, 119.1, 122.5, 124.4, 130.3, 148.7, 152.8, 153.7, 169.8; HRMS (ESI, +ve)  $m/z$  calcd. for C<sub>23</sub>H<sub>32</sub>NO<sub>6</sub> 418.2230, found: 418.2239 (M+H)<sup>+</sup>.

**(2*S*,5*S*,9*R*)-*tert*-Butyl 2-*tert*-butyl-8-(hydroxymethyl)-9-(4-methoxybenzyloxy)-6-oxo-3,7-dioxo-1-azaspiro[4.4]nonane-1-carboxylate (278)**



To a solution of (2*S*,4*S*)-4-benzyl 3-*tert*-butyl 2-*tert*-butyl-4-((*R*)-1-(4-methoxybenzyloxy)allyl)oxazolidine-3,4-dicarboxylate **ent-254k** (40 mg, 74.1  $\mu$ mol, 1 eq) in water/acetone (0.9 mL, 1:8) was added NMO (20 mg, 0.148 mmol, 2 eq) and a *t*BuOH solution of OsO<sub>4</sub> (47  $\mu$ L, 3.7  $\mu$ mol, 5 mol%) and allowed to stir at room temperature for 24 hours. Quenched with sat. NaHCO<sub>3</sub> solution and allowed to stir for 10 mins. Extracted with EtOAc (2  $\times$  15 mL), washed with brine (1  $\times$  25 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* and purified by flash chromatography (8:1 – 2:1 Pet/EtOAc) to afford the pure title compound as a colourless oil (42 mg, 100%).  $[\alpha]_D^{20} +33.7$  (*c* 1.75, CHCl<sub>3</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 3514, 2934, 2873, 1793, 1714, 1693, 1613; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>, 328K)  $\delta_H$  1.12 (9H, s), 1.46 (9H, s), 1.72 (1H, bs), 3.73 (1 H, app. d, *J* = 9.7 Hz), 3.82 (3H, s), 3.91 (1H, dd, *J* = 12.7, 2.4 Hz), 4.00 (1H, bs), 4.13 (1H, d, *J* = 8.2 Hz), 4.38 (1H, app. d, *J* = 10.8 Hz), 4.60–4.93 (3H, m), 5.21 (1H, bs), 6.90 (2H, d, *J* = 8.7 Hz), 7.26 (2H, d, *J* = 8.7 Hz); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>, 328K)  $\delta_C$  26.7, 28.1, 39.4, 55.2, 60.9, 69.1, 73.2, 75.4, 79.7, 82.5, 97.4, 114.1, 117.6, 129.1, 129.8, 152.4, 159.9, 171.9; HRMS (ESI, +ve) *m/z* calcd. for C<sub>24</sub>H<sub>36</sub>NO<sub>8</sub> 466.2441, found: 466.2452 (M+H)<sup>+</sup>.

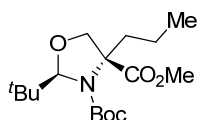
**(2*S*,5*S*,9*R*)-*tert*-Butyl 2-*tert*-butyl-9-(4-methoxybenzyloxy)-8-((4-nitrobenzoyloxy)methyl)-6-oxo-3,7-dioxo-1-azaspiro[4.4]nonane-1-carboxylate (280)**



To a solution of (2*S*,5*S*,9*R*)-*tert*-butyl 2-*tert*-butyl-8-(hydroxymethyl)-9-(4-methoxybenzyloxy)-6-oxo-3,7-dioxo-1-azaspiro[4.4]nonane-1-carboxylate **278** (34 mg, 59.2  $\mu$ mol, 1 eq) in DCM (10 mL) at room temperature was added DMAP (5 mol%), NEt<sub>3</sub> (13  $\mu$ L, 88.9  $\mu$ mol, 1.5 eq) and 4-nitrobenzoyl chloride (11 mg, 59.2  $\mu$ mol, 1 eq) and the reaction mixture stirred overnight. Quenched with water. Extracted with DCM (2  $\times$  10 mL) and the organics washed with 1M HCl (1  $\times$  25 mL), sat. NaHCO<sub>3</sub> (1  $\times$  25 mL), brine (1  $\times$  25 mL), dried over MgSO<sub>4</sub> and concentrated *in vacuo* and purified by

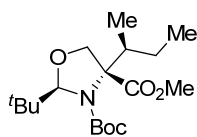
flash chromatography (2:1 Pet/EtOAc) to afford a white solid (23 mg, 64%). Recrystallised using DCM/Petrol 60-80 °C to afford clear crystals. Mpt: 173-174 °C;  $[\alpha]_D^{20} +70.1$  ( $c$  0.87,  $\text{CHCl}_3$ ); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2965, 2936, 2909, 2878, 1798, 1728, 1687, 1611;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , 328K)  $\delta_{\text{H}}$  1.17 (9H, s), 1.51 (9H, s), 3.80 (3H, s), 4.20 (1H, d,  $J = 8.2$  Hz), 4.24 (1H, m), 4.37 (1H, d,  $J = 11.2$  Hz), 4.49 (1H, app. d,  $J = 7.5$  Hz), 4.66 (1H, dd,  $J = 12.4, 2.5$  Hz), 4.71–4.83 (2H, m), 4.89–5.43 (2H, m), 6.85 (2H, app. d,  $J = 8.0$  Hz), 7.26 (2H, d,  $J = 8.0$  Hz), 8.29 (4H, bs);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  26.9, 28.2, 39.3, 55.2, 62.6, 68.7, 69.8, 73.3, 74.1, 82.6, 97.2, 114.1, 117.6, 123.3, 128.8, 129.8, 131.1, 134.8, 150.9, 152.4, 159.9, 164.2, 171.4; MS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{31}\text{H}_{38}\text{N}_2\text{O}_{11}\text{Na}$  637.2373, found: 637.2388 ( $\text{M}+\text{Na}$ ) $^+$ .

**(2*R*,4*S*)-3-*tert*-Butyl 4-methyl 2-*tert*-butyl-4-propyloxazolidine-3,4-dicarboxylate (281a)**



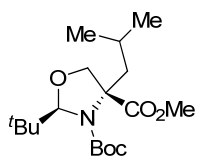
A mixture of (2*R*,4*S*)-3-*tert*-Butyl 4-methyl 4-allyl-2-*tert*-butyloxazolidine-3,4-dicarboxylate **266a** (192 mg, 0.59 mmol, 1 eq) and 10 mol% Pd/C (10 mg, 5 wt%) in MeOH (22 mL) was hydrogenated at atmospheric pressure for 90 minutes. Reaction mixture filtered through celite® and concentrated *in vacuo* to afford the title compound as a pale yellow oil (168 mg, 87%).  $[\alpha]_D -7.5$  ( $c$  1.2,  $\text{CH}_2\text{Cl}_2$ ); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2967, 2874, 1742, 1709;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  0.89 (3H, t,  $J = 7.3$  Hz), 0.95 (9H, s), 1.04-1.10 (1H, m), 1.40 (9H, s), 1.44-1.50 (1H, m), 1.89 (1H, td,  $J = 13.3, 4.3$  Hz), 2.33 (1H, bs), 3.70 (3H, s), 3.94 (1H, d,  $J = 8.6$  Hz), 4.21 (1H, dd,  $J = 1.5, 8.6$  Hz), 5.08 (1H, s);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  14.2, 16.3, 26.2, 27.9, 37.4, 39.4, 52.2, 68.9, 76.0, 80.5, 98.3, 153.4, 172.7; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{17}\text{H}_{31}\text{NO}_5\text{Na}$  352.2100, found: 352.2106 ( $\text{M}+\text{Na}$ ) $^+$ .

**(2*R*,4*S*)-3-*tert*-Butyl 4-methyl 4-(*sec*-butyl)-2-(*tert*-butyl)oxazolidine-3,4-dicarboxylate (281b)**



A mixture of (2*R*,4*S*)-3-*tert*-butyl 4-methyl 4-((*S*)-but-3-en-2-yl)-2-*tert*-butyloxazolidine-3,4-dicarboxylate **266b** (175 mg, 0.51 mmol, 1 eq) and 10 mol% Pd/C (9mg, 5 wt%) in MeOH (20 mL) was hydrogenated at atmospheric pressure for 90 minutes. Reaction mixture filtered through celite® and concentrated *in vacuo* to afford the title compound as a pale yellow oil (90 mg, 51%).  $[\alpha]_D -9.2$  (*c* 1.2, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2963, 2912, 2877, 1743, 1707, 1478; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_H$  0.87 (3H, d, *J* = 6.7 Hz), 0.91-1.01 (12H, m), 1.39-1.49 (11H, m), 2.68 (1H, bs), 3.73 (3H, s), 4.04 (1H, d, *J* = 8.8 Hz), 4.33 (1H, d, *J* = 8.8 Hz), 5.08 (1H, s); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_C$  13.1, 13.5, 26.5, 26.9, 28.1, 37.2, 39.0, 52.2, 71.1, 72.4, 80.7, 97.8, 153.5, 172.7; HRMS (ESI, +ve) *m/z* calcd. for C<sub>18</sub>H<sub>33</sub>NO<sub>5</sub>Na 366.2256, found: 366.2231 (M+Na)<sup>+</sup>.

**(2*R*,4*S*)-3-*tert*-Butyl 4-methyl 2-(*tert*-butyl)-4-isobutyloxazolidine-3,4-dicarboxylate (281c)**

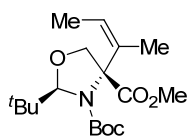


A mixture of (2*R*,4*S*)-3-*tert*-butyl 4-methyl 2-*tert*-butyl-4-(2-methylallyl)oxazolidine-3,4-dicarboxylate **266c** (85 mg, 0.25 mmol, 1 eq) and 10 mol% Pd/C (5mg, 5 wt%) in MeOH (9 mL) was hydrogenated at atmospheric pressure for 90 minutes. Reaction mixture filtered through celite® and concentrated *in vacuo* to afford the title compound as a pale yellow oil (56 mg, 66%).  $[\alpha]_D -3.6$  (*c* 1.1, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2958, 2915, 2873, 1744, 1706, 1478; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_H$  0.91 (3H, d, *J* = 6.6 Hz), 0.97-1.03 (12H, m), 1.44 (9H, s), 1.69-1.75 (1H, m), 1.90 (1H, dd, *J* = 14.2, 5.7



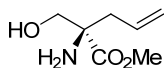
Hz), 2.27 (1H, d,  $J = 9.6$  Hz), 3.73 (3H, s), 4.03 (1H, d,  $J = 8.7$  Hz), 4.23 (1H, dd,  $J = 8.7, 1.5$  Hz), 5.15 (1H, s);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  23.6, 24.3, 24.6, 26.7, 28.2, 39.6, 42.3, 52.3, 69.0, 75.0, 80.7, 98.0, 153.0, 172.9; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{18}\text{H}_{33}\text{NO}_5\text{Na}$  366.2256, found: 366.2249 ( $\text{M}+\text{Na}$ ) $^{+}$ .

**(2R,4S)-3-*tert*-Butyl 4-methyl 4-((Z)-but-2-en-2-yl)-2-*tert*-butyloxazolidine-3,4-dicarboxylate (281d)**



A mixture of (2R,4S)-3-*tert*-butyl 4-methyl 4-(buta-2,3-dien-2-yl)-2-*tert*-butyloxazolidine-3,4-dicarboxylate **266d** (41 mg, 0.121 mmol, 1 eq) and 10 mol% Pd/C (4mg, 10 wt%) in MeOH (2mL) was hydrogenated at atmospheric pressure for 20 minutes. Reaction mixture filtered through celite® and concentrated *in vacuo*. Purified by flash chromatography (20:1 Pet/EtOAc) to afford the title compound as a colourless oil (33 mg, 80%).  $[\alpha]_{\text{D}} -71.1$  ( $c$  1.35,  $\text{CHCl}_3$ ); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2976, 2960, 2933, 2875, 1760, 1732, 1698;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  0.93 (9H, s), 1.44 (9H, s), 1.57 (3H, dd,  $J = 7.5, 1.4$  Hz), 1.71 (3H, app. t,  $J = 1.4$  Hz), 3.76 (3H, s), 4.23 (1H, d,  $J = 9.1$  Hz), 4.58 (1H, d,  $J = 9.1$  Hz), 5.34 (1H, s), 5.46 (1H, qd,  $J = 7.5, 1.4$  Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  13.8, 22.6, 26.2, 28.2, 39.0, 52.2, 70.8, 77.8, 80.4, 98.8, 124.2, 133.4, 153.5, 172.8; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{18}\text{H}_{32}\text{NO}_5$  342.2280, found: 342.2287 ( $\text{M}+\text{H}$ ) $^{+}$ .

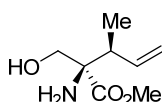
**(R)-Methyl 2-amino-2-(hydroxymethyl)pent-4-enoate (282a)**



(2R,4S)-3-*tert*-Butyl 4-methyl 4-allyl-2-*tert*-butyloxazolidine-3,4-dicarboxylate **266a** (110 mg, 0.336 mmol), MeOH (1.6 mL) and 6N HCl (1.12 mL, 6.72 mmol) were combined according to general procedure IX to afford the title compound as a colourless oil (43 mg, 80%).  $[\alpha]_{\text{D}} -5.6$  ( $c$  0.8,  $\text{CH}_2\text{Cl}_2$ ); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 3367,

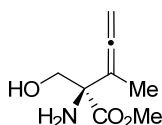
2954, 2254, 1733, 1642, 1594;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  2.23 (1H, dd,  $J = 13.7$ , 7.4 Hz), 2.47 (1H, dd,  $J = 13.7$ , 7.4 Hz), 2.55 (3H, bs), 3.49 (1H, d,  $J = 10.7$  Hz), 3.73 (3H, s), 3.78 (1H, d,  $J = 10.7$  Hz), 5.12 (1H, d,  $J = 5.8$  Hz), 5.15 (1H, s), 5.59-5.69 (1H, m);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  40.4, 52.4, 62.3, 67.8, 120.0, 131.6, 175.7; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_7\text{H}_{13}\text{NO}_3\text{Na}$  182.0793, found: 182.0781 ( $\text{M}+\text{Na}$ ) $^+$ .

**(2R,3S)-Methyl 2-amino-2-(hydroxymethyl)-3-methylpent-4-enoate (282b)**



(2R,4S)-3-*tert*-Butyl 4-methyl 4-((*S*)-but-3-en-2-yl)-2-*tert*-butyloxazolidine-3,4-dicarboxylate **266b** (110 mg, 0.322 mmol), MeOH (1.5 mL) and 6N HCl (1.07 mL, 6.44 mmol) were combined according to general procedure IX to afford the title compound as a yellow oil (25 mg, 45%).  $[\alpha]_{\text{D}} -49$  ( $c$  1.1,  $\text{CH}_2\text{Cl}_2$ ); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2970, 2957, 2253, 1730, 1595;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  0.97 (3H, d,  $J = 7.0$  Hz), 2.22 (3H, bs), 2.56 (1H, quint,  $J = 7.3$  Hz), 3.52 (1H, d,  $J = 10.8$  Hz), 3.77 (3H, s), 3.83 (1H, d,  $J = 10.8$  Hz), 5.06-5.16 (2H, m), 5.72 (1H, ddd,  $J = 16.9$ , 10.5, 8.6 Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  14.8, 42.9, 52.4, 65.2, 67.1, 117.2, 137.9, 175.4; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_8\text{H}_{15}\text{NO}_3\text{Na}$  196.0950, found: 196.0939 ( $\text{M}+\text{Na}$ ) $^+$ .

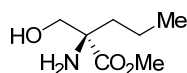
**(R)-Methyl 2-amino-2-(hydroxymethyl)-3-methylpenta-3,4-dienoate (282c)**



(2R,4S)-3-*tert*-Butyl 4-methyl 4-(buta-2,3-dien-2-yl)-2-*tert*-butyloxazolidine-3,4-dicarboxylate **266d** (100 mg, 0.295 mmol), MeOH (1.5 mL) and 6N HCl (1.17 mL, 5.90 mmol) were combined according to general procedure IX to afford the title compound as a yellow oil (22 mg, 44%).  $[\alpha]_{\text{D}} -32$  ( $c$  0.7,  $\text{CH}_2\text{Cl}_2$ ); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 3365, 2954, 2252, 1957, 1731, 1584;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  1.73 (3H, t,  $J = 3.4$  Hz), 2.59 (3H, bs), 3.60 (1H, d,  $J = 10.7$  Hz), 3.78 (3H, s), 3.98 (1H, d,  $J = 10.7$  Hz) 4.82-

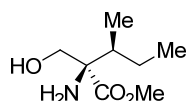
4.92 (2H, m);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  14.6, 52.7, 63.4, 66.0, 78.2, 99.9, 173.7, 205.6; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_8\text{H}_{13}\text{NO}_3\text{Na}$  194.0793, found: 194.0778 ( $\text{M}+\text{Na}$ ) $^+$ .

**(R)-Methyl 2-amino-2-(hydroxymethyl)pentanoate (282d)**

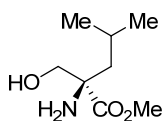


(2*R*,4*S*)-3-*tert*-Butyl 4-methyl 2-*tert*-butyl-4-propyloxazolidine-3,4-dicarboxylate **281a** (110 mg, 0.334 mmol), MeOH (1.6 mL) and 6N HCl (1.32 mL, 6.68 mmol) were combined according to general procedure IX to afford the title compound as a yellow oil (39 mg, 73%).  $[\alpha]_{\text{D}} -25.7$  ( $c$  0.7,  $\text{CH}_2\text{Cl}_2$ ); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 3358, 3304, 2960, 2876, 1737, 1564;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  0.92 (3H, t,  $J = 7.3$  Hz), 1.14-1.22 (1H, m), 1.34-1.42 (1H, m), 1.48 (1H, td,  $J = 13.0, 4.4$  Hz), 1.69 (1H, bs), 2.19 (3H, bs), 3.47 (1H, d,  $J = 8.9$  Hz), 3.76 (3H, s), 3.82 (1H, bs);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  14.2, 16.9, 38.1, 52.5, 63.1, 67.7, 175.6; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_7\text{H}_{15}\text{NO}_3\text{Na}$  184.0950, found: 184.0943 ( $\text{M}+\text{Na}$ ) $^+$ .

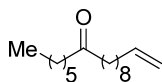
**(2R,3S)-Methyl 2-amino-2-(hydroxymethyl)-3-methylpentanoate (282e)**



(2*R*,4*S*)-3-*tert*-Butyl 4-methyl 4-(*sec*-butyl)-2-(*tert*-butyl)oxazolidine-3,4-dicarboxylate **281b** (75 mg, 0.218 mmol), MeOH (1.5 mL) and 6N HCl (867  $\mu\text{L}$ , 4.37 mmol) were combined according to general procedure IX to afford the title compound as a yellow oil (23 mg, 59%).  $[\alpha]_{\text{D}} -43.6$  ( $c$  1.1,  $\text{CH}_2\text{Cl}_2$ ); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 3301, 2965, 2939, 2878, 1730, 1596;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  0.87 (3H, d,  $J = 6.9$  Hz), 0.92 (3H, t,  $J = 7.2$  Hz), 0.98-1.04 (1H, m), 1.52-1.58 (1H, m), 1.64-1.70 (1H, m), 2.48 (3H, bs), 3.57 (1H, d,  $J = 10.7$  Hz), 3.75 (3H, s), 3.87 (1H, d,  $J = 10.7$  Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  12.3, 13.5, 23.4, 40.4, 52.3, 66.3, 66.5, 175.8; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_8\text{H}_{17}\text{NO}_3\text{Na}$  198.1106, found: 198.1077 ( $\text{M}+\text{Na}$ ) $^+$ .

**(R)-Methyl 2-amino-2-(hydroxymethyl)-4-methylpentanoate (282f)**

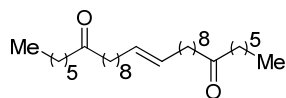
(2*R*,4*S*)-3-*tert*-Butyl 4-methyl 2-(*tert*-butyl)-4-isobutyloxazolidine-3,4-dicarboxylate **281c** (56 mg, 0.163 mmol), MeOH (0.8 mL) and 6N HCl (647  $\mu$ L, 3.26 mmol) were combined according to general procedure IX to afford the title compound as a pale yellow oil (20 mg, 71%).  $[\alpha]_D^{25}$  -36 (*c* 1.0, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 3367, 3302, 2955, 2873, 1732, 1598; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_H$  0.84 (3H, d, *J* = 6.5 Hz), 0.94 (3H, d, *J* = 6.5 Hz), 1.47 (1H, dd, *J* = 13.9, 5.0 Hz), 1.61-1.75 (2H, m), 2.41 (3H, bs), 3.41 (1H, d, *J* = 10.4 Hz), 3.74 (3H, s), 3.77 (1H, d, *J* = 10.4 Hz); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_C$  22.8, 23.9, 24.4, 44.6, 52.3, 62.3, 69.1, 176.6; HRMS (ESI, +ve) *m/z* calcd. for C<sub>8</sub>H<sub>17</sub>NO<sub>3</sub>Na 198.1106, found: 198.1113 (M+Na)<sup>+</sup>.

**Heptadec-16-en-7-one (286)**

To the orange/red solution of Fe(acac)<sub>3</sub> (110 mg, 0.300 mmol, 3 mol%) in THF (100 mL) at -78 °C was added hexyl magnesium bromide (2.0M, 6.50 mL, 13.0 mmol) and the solution turned dark brown. The reaction mixture was allowed to stir for 30 minutes before undecanoyl chloride (2.15 mL, 10.0 mmol) was added *via* syringe and stirred at -78 °C for 1 hour. Quenched with NH<sub>4</sub>Cl (sat.) (75 mL) and allowed to warm to room temperature and extracted with Et<sub>2</sub>O (3  $\times$  75 mL), dried over MgSO<sub>4</sub> and concentrated *in vacuo* to afford the crude ketone. Purification by flash chromatography (20:1 Pet/EtOAc) affords the title compound as a white solid (2.44 g, 97%). Mpt: 32-34 °C (lit.<sup>239</sup> 33-34 °C); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2957, 2918, 2848, 1698; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta_H$  0.88 (3H, t, *J* = 6.5 Hz), 1.28 (14H, s), 1.35-1.43 (2H, m), 1.51-1.61 (4H, m), 2.04 (2H, q, *J* = 6.8 Hz), 2.38 (4H, t, *J* = 7.4 Hz), 4.93 (1H, d, *J* = 10.1 Hz), 4.99 (1H, d, *J* = 17.2 Hz), 5.76-7.86 (1H, m); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta_C$  14.0, 22.5, 23.8, 23.9, 28.9 ( $\times$ 2), 29.0, 29.2, 29.3 ( $\times$ 2), 31.6, 33.8, 42.8 ( $\times$ 2), 114.1, 139.1, 211.6;

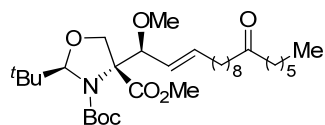
MS (ESI, +ve)  $m/z$  calcd. for  $C_{17}H_{32}ONa$  275.2351, found: 275.2353 ( $M+Na$ )<sup>+</sup>. All data in accordance with literature precedence.<sup>239</sup>

**(E)-Dotriacont-16-ene-7,26-dione (289)**



To a solution of heptadec-16-en-7-one **286** (250 mg, 1 mmol, 2 eq) in DCM (5 mL) was added Grubbs II (11 mg, 0.0125 mmol, 2.5 mol%) and heated at reflux for 3 days. Reaction mixture concentrated *in vacuo* and the residue purified by flash chromatography (20:1 Pet/EtOAc) to afford the title compound as a white solid (197 mg, 83%). Mpt: 66–67 °C; FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2956, 2918, 2848, 1699; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta_H$  0.88 (6H, t,  $J$  = 6.9 Hz), 1.22–1.36 (32H, m), 1.52–1.61 (8H, m), 1.92–2.00 (4H, m), 2.36–2.41 (8H, m), 5.36–5.39 (2H, m); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta_C$  14.0, 22.5, 23.8, 23.9, 28.9, 29.1, 29.3 ( $\times 3$ ), 29.4, 29.6, 31.6, 32.6, 42.8, 130.3, 211.7; MS (ESI, +ve)  $m/z$  calcd. for  $C_{32}H_{60}O_2Na$  499.4491, found: 499.4474 ( $M+Na$ )<sup>+</sup>.

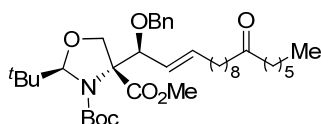
**(2R,4R)-3-tert-Butyl 4-methyl 2-tert-butyl-4-((S,E)-1-methoxy-12-oxooctadec-2-enyl) oxazolidine-3,4-dicarboxylate (288a)**



To a solution of (2R,4R)-3-tert-butyl 4-methyl 2-tert-butyl-4-((S)-1-methoxyallyl)oxazolidine-3,4-dicarboxylate **252a** (64 mg, 0.178 mmol) and (E)-dotriacont-16-ene-7,26-dione **289** (85 mg, 0.178 mmol) in DCM (500  $\mu$ L) was added Hoveyda-Grubbs II (6 mg, 0.009 mmol, 5 mol%) and heated at reflux for 72 hours. Reaction mixture concentrated *in vacuo* and the residue purified by flash chromatography (15:1 Pet/EtOAc) to afford the title compound as a colourless oil (51 mg, 48%).  $[\alpha]_D^{20}$  -12.5 ( $c$  0.8, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2957, 2932, 2858, 1740, 1702; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_H$  0.87–0.98 (12H, m), 1.24–1.42 (16H, m), 1.51

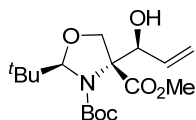
(9H, s), 1.54–1.63 (4H, m), 2.06 (2H, q,  $J = 6.8$  Hz), 2.38 (4H, t,  $J = 7.4$  Hz), 3.24 (3H, s), 3.71 (3H, s), 4.15 (1H, d,  $J = 8.3$  Hz), 4.41 (1H, d,  $J = 8.3$  Hz), 4.79 (1H, d,  $J = 6.5$  Hz), 5.13 (1H, s), 5.21 (1H, dd,  $J = 15.5, 6.5$  Hz), 5.76 (1H, dt,  $J = 15.5, 6.8$  Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  13.8, 22.4, 23.8 ( $\times 2$ ), 26.1, 28.2, 28.9, 29.1 ( $\times 2$ ), 29.2 ( $\times 3$ ), 31.5, 32.2, 38.1, 42.7 ( $\times 2$ ), 52.0, 56.1, 69.6, 72.7, 78.8, 80.6, 98.1, 125.3, 137.4, 153.8, 171.0, 211.0; MS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{33}\text{H}_{59}\text{NO}_7\text{Na}$  604.4189, found: 604.4131 ( $\text{M}+\text{Na}$ ) $^{+}$ .

**(2*R*,4*R*)-3-*tert*-Butyl 4-methyl 2-*tert*-butyl-4-((*S*,*E*)-1-(benzyloxy)-12-oxooctadec-2-enyl) oxazolidine-3,4-dicarboxylate (**288j**)**



To a solution of (2*R*,4*R*)-3-*tert*-butyl 4-methyl 2-*tert*-butyl-4-((*S*)-1-benzyloxyallyl)oxazolidine-3,4-dicarboxylate **252j** (87 mg, 0.200 mmol) and (*E*)-dotriacont-16-ene-7,26-dione **289** (76 mg, 0.160 mmol) in DCM (500  $\mu\text{L}$ ) was added Hoveyda-Grubbs II (6 mg, 0.010 mmol, 5 mol%) and heated at reflux for 4 days. Reaction mixture concentrated *in vacuo* and the residue purified by flash chromatography (15:1 Pet/EtOAc) to afford the title compound as a colourless oil (29 mg, 22%). *N.B.* Unable to isolate cleanly due to co-elution of **252j** and **288j**. Furthermore, due to poor solubility of **289**, and poor consumption during the reaction, this co-elutes across entire column despite large  $R_f$  difference.

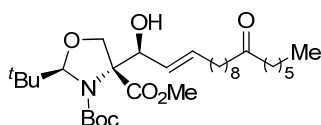
**(2*R*,4*R*)-4-Benzyl 3-*tert*-butyl 2-*tert*-butyl-4-((*S*)-1-hydroxyallyl)oxazolidine-3,4-dicarboxylate (**290**)**



To a solution of (2*R*,4*R*)-3-*tert*-butyl 4-methyl 2-*tert*-butyl-4-((*S*)-1-(4-methoxybenzyloxy)allyl)oxazolidine-3,4-dicarboxylate **252k** (185 mg, 0.400 mmol, 1

eq) in DCM/H<sub>2</sub>O (18:1, 4.0 mL) was added DDQ (114 mg, 0.50 mmol, 1.25 eq) and stirred at room temperature for 2 hours. The precipitate formed was removed by filtration, and the filtrate was concentrated *in vacuo* to afford the crude allylic alcohol. Purified by flash chromatography (8:1 Pet/EtOAc) to afford the title compound (106 mg, 77% NMR corrected yield\*). FTIR (film/cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 3352, 2972, 2877, 1761, 1735, 1680; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  0.94 (9H, s), 1.46 (9H, s), 3.83 (3H, s), 4.05 (1H, d,  $J = 9.7$  Hz), 4.48 (1H, d,  $J = 9.7$  Hz), 4.54 (1H, app. dt,  $J = 11.2, 1.8$  Hz), 5.19 (1H, s), 5.33 (1H, dt,  $J = 10.7, 1.8$  Hz), 5.52 (1H, dt,  $J = 17.1, 1.8$  Hz), 5.83 (1H, bs), 5.95 (1H, ddd,  $J = 17.1, 10.7, 4.0$  Hz); HRMS (ESI, +ve)  $m/z$  calcd. for C<sub>17</sub>H<sub>29</sub>NO<sub>6</sub>Na 366.1893, found: 366.1885 (M+Na)<sup>+</sup>.

**(2*R*,4*R*)-3-*tert*-Butyl 4-methyl 2-*tert*-butyl-4-((*S*,*E*)-1-hydroxy-12-oxooctadec-2-enyl)oxazolidine-3,4-dicarboxylate (291)**

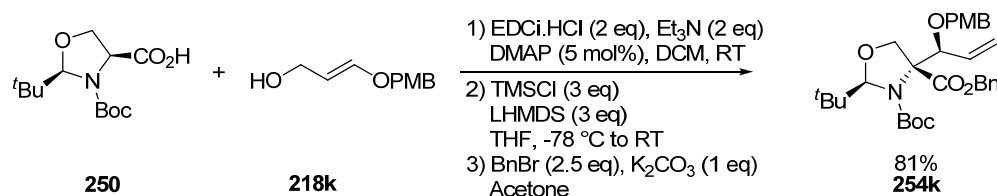


To a solution of (2*R*,4*R*)-3-*tert*-butyl 4-methyl 2-*tert*-butyl-4-((*S*)-1-hydroxyallyl)oxazolidine-3,4-dicarboxylate **290** (45mg, 0.103 mmol) and (*E*)-dotriacont-16-ene-7,26-dione **289** (49 mg, 0.103 mmol) in DCM (500  $\mu$ L) was added Hoveyda-Grubbs II (3.2 mg, 0.0052 mmol, 5 mol%) and heated at reflux for 30 hours. Reaction mixture concentrated *in vacuo* and the residue purified by column chromatography (15:1 to 4:1 Pet/EtOAc) to afford the title compound as a colourless oil (48 mg, 83%).  $[\alpha]_{\text{D}}^{20}$  -10.7 ( $c$  0.75, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 3377, 2954, 2930, 2857, 1762, 1737, 1714, 1686; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  0.88 (3H, t,  $J = 6.9$  Hz), 0.94 (9H, s), 1.24–1.34 (14H, m), 1.34–1.43 (2H, m), 1.49 (9H, s), 1.53–1.60 (4H, m), 2.02–2.09 (2H, m), 2.39 (4H, t,  $J = 7.5$  Hz), 3.82 (3H, s), 4.00 (1H, d,  $J = 9.4$  Hz), 4.46 (2H, app. d,  $J = 9.4$  Hz), 5.17 (1H, s), 5.46 (1H, dd,  $J = 15.4, 5.3$  Hz), 5.70 (1H, bs), 5.83–5.91 (1H, m); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  14.0, 22.5, 23.8, 26.6, 28.2, 28.9 ( $\times 2$ ), 29.1, 29.2, 29.3 ( $\times 2$ ), 29.4, 31.6, 32.4, 39.3, 42.8 ( $\times 2$ ), 52.6, 74.2, 75.1, 77.8, 82.2,

\* *p*-Anisaldehyde still present. Used in cross-metathesis in this crude form.

99.4, 125.2, 135.0, 155.5, 171.2, 211.7; MS (ESI, +ve)  $m/z$  calcd. for  $C_{32}H_{57}NO_7Na$  590.4032, found: 590.4039 ( $M+Na$ )<sup>+</sup>.

**(2*R*,4*R*)-4-Benzyl 3-*tert*-butyl 2-*tert*-butyl-4-((*S*)-1-(4-methoxybenzyloxy)allyl)oxazolidine-3,4-dicarboxylate (**254** by Preparative Scale Synthesis)**

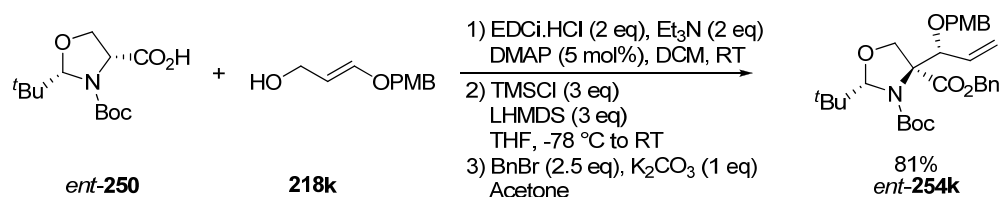


To a stirred solution of L-Boc oxazolidine carboxylic acid **250** (2.19 g, 8.00 mmol, 2 eq) in DCM (125 mL) was added EDCi.HCl (1.53 g, 8.00 mmol, 2 eq), triethylamine (1.12 mL, 8.00 mmol, 2 eq), catalytic DMAP (5 mol%) and (*E*)-3-(4-methoxybenzyloxy)prop-2-en-1-ol **218k** (925 mg, 4.00 mmol, 1 eq). The reaction was stirred at room temperature for 2 hours then washed with  $\text{NaHCO}_3$  (sat) ( $3 \times 50$  mL), 10% citric acid ( $1 \times 50$  mL), brine ( $1 \times 50$  mL) and dried over  $\text{Na}_2\text{SO}_4$ . Concentration *in vacuo* affords the crude oxazolidine ester (1.80 g, quant).

To a stirred solution of the crude oxazolidine ester (1.80 g, 4.00 mmol, 1 eq) in THF (18.0 mL) at  $-78$  °C was added TMSCl (1.53 mL, 12.0 mmol, 3 eq). After 10 mins LHMDs (1M, 12.0 mL, 12.0 mmol, 3 eq) was added *via* syringe pump at an addition rate of  $10 \text{ mL hr}^{-1}$  and reaction mixture allowed to warm to room temperature after a period of 30 mins, and stirred for 18 hours. The reaction was quenched by the addition of 1N HCl and brine solution (1:1) and extracted with DCM ( $3 \times 50$  mL), dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo* to afford the crude acid. Residue dissolved in acetone (35.0 mL), and  $\text{K}_2\text{CO}_3$  (552 mg, 4.00 mmol, 1 eq) and BnBr (1.19 mL, 10.0 mmol, 2.5 eq) added and reaction mixture stirred for 4 hours. Partitioned between between EtOAc and  $\text{NaHCO}_3$  (sat) and washed with  $\text{NaHCO}_3$  (sat) ( $3 \times 50$  mL), brine ( $1 \times 50$  mL) and dried over  $\text{Na}_2\text{SO}_4$ . Concentration *in vacuo* affords the crude ester. Purification by flash chromatography (10:1 Pet/EtOAc) affords the title compound *ent*-**254k** as a colourless oil (1.70 g, 79%, dr >99:1). All data as previously stated.



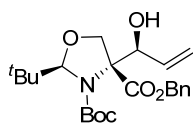
**(2*S*,4*S*)-4-Benzyl 3-*tert*-butyl 2-*tert*-butyl-4-((*R*)-1-(4-methoxybenzyloxy)allyl)oxazolidine-3,4-dicarboxylate (*ent*-254k by Preparative Scale Synthesis)**



To a stirred solution of D-Boc oxazolidine carboxylic acid *ent*-**250** (2.19 g, 8.00 mmol, 2 eq) in DCM (125 mL) was added EDCi.HCl (1.53 g, 8.00 mmol, 2 eq), triethylamine (1.12 mL, 8.00 mmol, 2 eq), catalytic DMAP (5 mol%) and (*E*)-3-(4-methoxybenzyloxy)prop-2-en-1-ol **218k** (925 mg, 4.00 mmol, 1 eq). The reaction was stirred at room temperature for 2 hours then washed with NaHCO<sub>3</sub> (sat) (3 × 50 mL), 10% citric acid (1 × 50 mL), brine (1 × 50 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration *in vacuo* affords the crude oxazolidine ester (1.80g, quant).

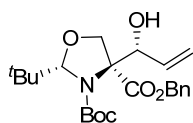
To a stirred solution of the crude oxazolidine ester (1.80 g, 4.00 mmol, 1 eq) in THF (18.0 mL) at -78 °C was added TMSCl (1.53 mL, 12.0 mmol, 3 eq). After 10 mins LHMDS (1M, 12.0 mL, 12.0 mmol, 3 eq) was added *via* syringe pump at an addition rate of 10 mL hr<sup>-1</sup> and reaction mixture allowed to warm to room temperature after a period of 30 mins, and stirred for 18 hours. The reaction was quenched by the addition of 1N HCl and brine solution (1:1) and extracted with DCM (3 × 50 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to afford the crude acid. Residue dissolved in acetone (35.0 mL), and K<sub>2</sub>CO<sub>3</sub> (552 mg, 4.00 mmol, 1 eq) and BnBr (1.19 mL, 10.0 mmol, 2.5 eq) added and reaction mixture stirred for 4 hours. Partitioned between between EtOAc and NaHCO<sub>3</sub> (sat) and washed with NaHCO<sub>3</sub> (sat) (3 × 50 mL), brine (1 × 50 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration *in vacuo* affords the crude ester. Purification by flash chromatography (10:1 Pet/EtOAc) affords the title compound *ent*-**254k** as a colourless oil (1.75 g, 81%, dr >99:1). All data as previously stated.

**(2*R*,4*R*)-4-Benzyl 3-*tert*-butyl 2-*tert*-butyl-4-((*S*)-1-hydroxyallyl)oxazolidine-3,4-dicarboxylate (292)**



To a solution of (2*R*,4*R*)-4-benzyl 3-*tert*-butyl 2-*tert*-butyl-4-((*S*)-1-(4-methoxybenzyloxy)allyl)oxazolidine-3,4-dicarboxylate **254k** (393 mg, 0.728 mmol, 1 eq) in DCM/H<sub>2</sub>O (18:1, 6.1 mL) was added DDQ (207 mg, 0.910 mmol, 1.25 eq) and stirred at room temperature for 2 hours. The precipitate formed was removed by filtration, and the filtrate was concentrated *in vacuo* to afford the crude allylic alcohol (390 mg, 89% NMR corrected yield<sup>†</sup>). Residue dissolved in MeOH (5 mL) and added dropwise to an ice-cold solution of sodium borohydride (82 mg, 2.18 mmol, 3 eq) in MeOH (20 mL) and reaction allowed to stir at 0 °C for 2 hours. Partitioned between water and DCM and the aqueous extracted with DCM (3 × 25 mL). The organics were combined and washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. Purified by flash chromatography (10:1 Pet/EtOAc) to afford the pure title compound as a colourless oil (225 mg, 74%). [ $\alpha$ ]<sub>D</sub><sup>20</sup> -33.8 (*c* 2.1, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 3349, 2973, 2910, 2876, 1760, 1734, 1682; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  0.89 (9H, s), 1.47 (9H, s), 4.06 (1H, d, *J* = 9.7 Hz), 4.48 (1H, d, *J* = 9.7 Hz), 4.57–4.62 (1H, m), 5.19 (1H, s), 5.22 (1H, d, *J* = 12.4 Hz), 5.31–5.37 (2H, m), 5.54 (1H, dt, *J* = 17.0, 1.8 Hz), 5.89 (1H, bs), 5.96 (1H, ddd, *J* = 17.0, 10.7, 4.0 Hz), 7.29–7.39 (3H, m), 7.39–7.43 (2H, m); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  26.6, 28.1, 39.3, 67.4, 74.0, 75.2, 78.2, 82.4, 99.4, 118.0, 128.2, 128.3, 128.5, 133.6, 135.4, 155.5, 170.2; HRMS (ESI, +ve) *m/z* calcd. for C<sub>23</sub>H<sub>33</sub>NO<sub>6</sub>Na 442.2206, found: 442.2207 (M+Na)<sup>+</sup>.

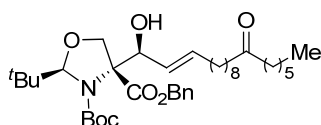
**(2*S*,4*S*)-4-Benzyl 3-*tert*-butyl 2-*tert*-butyl-4-((*R*)-1-hydroxyallyl)oxazolidine-3,4-dicarboxylate (*ent*-292)**



<sup>†</sup> *p*-Anisaldehyde still present. Subsequent sodium borohydride reduction to 4-methoxybenzyl alcohol allows purification by flash chromatography.

To a solution of (2*S*,4*S*)-4-benzyl 3-*tert*-butyl 2-*tert*-butyl-4-((*R*)-1-(4-methoxybenzyloxy)allyl)oxazolidine-3,4-dicarboxylate **ent-254k** (562 mg, 1.04 mmol, 1 eq) in DCM/H<sub>2</sub>O (18:1, 8.0 mL) was added DDQ (295 mg, 1.30 mmol, 1.25 eq) and stirred at room temperature for 2 hours. The precipitate formed was removed by filtration, and the filtrate was concentrated *in vacuo* to afford the crude allylic alcohol (390 mg, 89% NMR corrected yield<sup>†</sup>). Residue dissolved in MeOH (5 mL) and added dropwise to an ice-cold solution of sodium borohydride (118 mg, 3.12 mmol, 3 eq) in MeOH (30 mL) and reaction allowed to stir at 0 °C for 2 hours. Partitioned between water and DCM and the aqueous extracted with DCM (3 × 25 mL). The organics were combined and washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. Purified by flash chromatography (10:1 Pet/EtOAc) to afford the pure title compound as a colourless oil (324 mg, 74%). [ $\alpha$ ]<sub>D</sub><sup>20</sup> +32.5 (*c* 2.1, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 3349, 2973, 2910, 2876, 1760, 1734, 1682; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  0.89 (9H, s), 1.47 (9H, s), 4.06 (1H, d, *J* = 9.7 Hz), 4.48 (1H, d, *J* = 9.7 Hz), 4.57–4.62 (1H, m), 5.19 (1H, s), 5.22 (1H, d, *J* = 12.4 Hz), 5.31–5.37 (2H, m), 5.54 (1H, dt, *J* = 17.0, 1.8 Hz), 5.89 (1H, bs), 5.96 (1H, ddd, *J* = 17.0, 10.7, 4.0 Hz), 7.29–7.39 (3H, m), 7.39–7.43 (2H, m); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  26.6, 28.1, 39.3, 67.4, 74.0, 75.2, 78.2, 82.4, 99.4, 118.0, 128.2, 128.3, 128.5, 133.6, 135.4, 155.5, 170.2; HRMS (ESI, +ve) *m/z* calcd. for C<sub>23</sub>H<sub>33</sub>NO<sub>6</sub>Na 442.2206, found: 442.2207 (M+Na)<sup>+</sup>.

**(2*R*,4*R*)-4-Benzyl 3-*tert*-butyl 2-*tert*-butyl-4-((*S*,*E*)-1-hydroxy-12-oxooctadec-2-enyl)oxazolidine-3,4-dicarboxylate (293)**

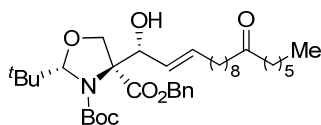


To a solution of (2*R*,4*R*)-4-benzyl 3-*tert*-butyl 2-*tert*-butyl-4-((*S*)-1-hydroxyallyl)oxazolidine-3,4-dicarboxylate **254k** (324 mg, 0.772 mmol, 1 eq) and (*E*)-dotriacont-16-ene-7,26-dione **289** (368 mg, 0.772 mmol, 1 eq) in DCM (1.0 mL) was added Hoveyda-Grubbs II (24.2 mg, 0.0386 mmol, 5 mol%) and heated at reflux for 24 hours. Reaction mixture concentrated *in vacuo* and the residue purified by flash

<sup>†</sup> *p*-Anisaldehyde still present. Subsequent sodium borohydride reduction to 4-methoxybenzyl alcohol allows purification by flash chromatography.

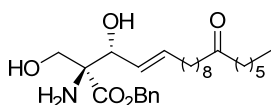
chromatography (15:1 Pet/EtOAc) to afford the title compound as a colourless oil (328 mg, 66%).  $[\alpha]_D^{20}$  -12.3 (*c* 2.2, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 3378, 2957, 2929, 2854, 1760, 1731, 1707, 1683; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta_H$  0.82–0.92 (12H, m), 1.22–1.33 (14H, m), 1.33–1.42 (2H, m), 1.47 (9H, s), 1.52–1.61 (4H, m), 2.00–2.08 (2H, m), 2.38 (4H, t, *J* = 7.4 Hz), 4.00 (1H, d, *J* = 9.5 Hz), 4.46 (1H, d, *J* = 9.4 Hz), 4.51 (1H, bs), 5.16 (1H, s), 5.20 (1H, d, *J* = 12.1 Hz), 5.31 (1H, d, *J* = 12.1 Hz), 5.47 (1H, dd, *J* = 15.4, 5.2 Hz), 5.77 (1H, bs), 5.83–5.92 (1H, m), 7.28–7.37 (3H, m), 7.37–7.42 (2H, m); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta_C$  14.0, 22.5, 23.8, 26.5 (×2), 28.2, 28.9 (×2), 29.0, 29.3 (×2), 29.4, 31.6, 32.4, 39.2, 42.8 (×2), 67.3, 74.1, 75.1, 77.3, 77.8, 82.1, 99.4, 125.1, 128.2, 128.4, 134.0, 135.5, 155.4, 170.6, 211.6; MS (ESI, +ve) *m/z* calcd. for C<sub>38</sub>H<sub>62</sub>NO<sub>7</sub> 644.4526, found: 644.4533 (M+H)<sup>+</sup>.

**(2*S*,4*S*)-4-Benzyl 3-*tert*-butyl 2-*tert*-butyl-4-((*R*,*E*)-1-hydroxy-12-oxooctadec-2-enyl)oxazolidine-3,4-dicarboxylate (*ent*-293)**



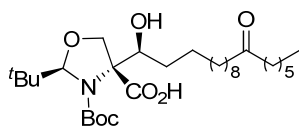
To a solution of (2*S*,4*S*)-4-benzyl 3-*tert*-butyl 2-*tert*-butyl-4-((*R*)-1-hydroxyallyl)oxazolidine-3,4-dicarboxylate *ent*-293 (125 mg, 0.297 mmol, 1 eq) and (*E*)-Dotriacont-16-ene-7,26-dione **289** (142 mg, 0.297 mmol, 1 eq) in DCM (1.0 mL) was added Hoveyda-Grubbs II (9.3 mg, 0.0149 mmol, 5 mol%) and heated at reflux for 24 hours. Reaction mixture concentrated *in vacuo* and the residue purified by flash chromatography (15:1 Pet/EtOAc) to afford the title compound as a colourless oil (144 mg, 75%).  $[\alpha]_D^{20}$  +12.0 (*c* 2, CH<sub>2</sub>Cl<sub>2</sub>). All other data as previously stated.

**(2*S*,3*R*,*E*)-Benzyl 2-amino-3-hydroxy-2-(hydroxymethyl)-14-oxoicos-4-enoate (*ent*-294)**



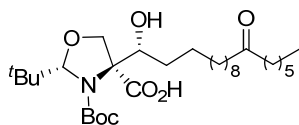
(2*S*,4*S*)-4-Benzyl 3-*tert*-butyl 2-*tert*-butyl-4-((*R*,*E*)-1-hydroxy-12-oxooctadec-2-enyl)oxazolidine-3,4-dicarboxylate **ent-293** (73 mg, 0.113 mmol, 1.0 eq), MeOH (2.0 mL) and 6N HCl (378  $\mu$ L, 2.27 mmol, 20 eq) were combined according to general procedure IX (reaction time: 6 hours) to afford the title compound as a pale yellow oil (40.4 mg, 75%).  $[\alpha]_D^{20} +16.0$  ( $c$  1, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 3359, 2926, 2854, 1739, 1711, 1587; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_H$  0.89 (3H, t,  $J$  = 6.7 Hz), 1.22–1.38 (16H, m), 1.50–1.62 (4H, m), 2.01 (2H, q,  $J$  = 7.0 Hz), 2.39 (4H, t,  $J$  = 7.4 Hz), 2.93 (4H, bs), 3.65 (1H, d,  $J$  = 11.2 Hz), 3.89 (1H, d,  $J$  = 11.2 Hz), 4.28 (1H, d,  $J$  = 7.4 Hz), 5.23 (2H, s), 5.45 (1H, dd,  $J$  = 15.4, 7.4 Hz), 5.73 (1H, dt,  $J$  = 15.4, 7.0 Hz), 7.31–7.41 (5H, m); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_C$  14.0, 22.5, 23.8 ( $\times 2$ ), 28.9 ( $\times 2$ ), 29.0, 29.2 ( $\times 2$ ), 29.3, 31.6, 32.2, 42.8 ( $\times 2$ ), 65.0, 66.5, 67.4, 75.0, 126.3, 128.2, 128.5, 128.6, 135.4, 136.3, 173.6, 211.9; HRMS (ESI, +ve)  $m/z$  calcd. for C<sub>28</sub>H<sub>45</sub>NO<sub>5</sub>Na 498.3195, found: 498.3173 (M+Na)<sup>+</sup>.

**(2*R*,4*R*)-3-(*tert*-Butoxycarbonyl)-2-*tert*-butyl-4-((*S*)-1-hydroxy-12-oxooctadecyl)oxazolidine-4-carboxylic acid (**295**)**



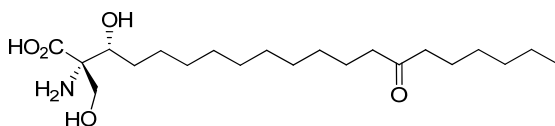
A mixture of (2*R*,4*R*)-4-benzyl 3-*tert*-butyl 2-*tert*-butyl-4-((*S*,*E*)-1-hydroxy-12-oxooctadec-2-enyl)oxazolidine-3,4-dicarboxylate **293** (120 mg, 0.186 mmol) and 10 mol% Pd/C (12 mg, 10 wt%) in EtOH (5.0 mL) was hydrogenated at atmospheric pressure for 1 hours. Reaction mixture filtered through celite® and concentrated *in vacuo* to afford the title compound as a pale yellow oil (103 mg, 100%).  $[\alpha]_D^{20} -35.0$  ( $c$  2, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 3408, 2954, 2926, 2855, 1760, 1712, 1679, 1615; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta_H$  0.88 (3H, t,  $J$  = 6.9 Hz), 0.94 (9H, s), 1.21–1.41 (20H, m), 1.47–1.66 (15H, m), 2.39 (4H, t,  $J$  = 7.5 Hz), 4.05 (1H, d,  $J$  = 9.7 Hz), 4.27 (1H, d,  $J$  = 9.6 Hz), 4.58 (1H, d,  $J$  = 9.7 Hz), 5.20 (1H, s); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta_C$  14.0, 22.5, 23.9 ( $\times 2$ ), 26.4, 28.1, 28.9, 29.2, 29.3, 29.4 ( $\times 4$ ), 31.5 ( $\times 2$ ), 31.6, 39.0, 42.8 ( $\times 2$ ), 72.4, 73.5, 74.2, 84.0, 98.6, 157.3, 171.4, 211.9; HRMS (ESI, +ve)  $m/z$  calcd. for C<sub>31</sub>H<sub>56</sub>NO<sub>7</sub> 554.4057, found: 554.4051 (M-H)<sup>+</sup>.

**(2*S*,4*S*)-3-(*tert*-Butoxycarbonyl)-2-*tert*-butyl-4-((*R*)-1-hydroxy-12-oxooctadecyl)oxazolidine-4-carboxylic acid (*ent*-295)**



A mixture of (2*S*,4*S*)-4-benzyl 3-*tert*-butyl 2-*tert*-butyl-4-((*R*,*E*)-1-hydroxy-12-oxooctadec-2-enyl)oxazolidine-3,4-dicarboxylate *ent*-293 (100 mg, 0.155 mmol) and 10 mol% Pd/C (10 mg, 10 wt%) in EtOH (5.0 mL) was hydrogenated at atmospheric pressure for 1 hours. Reaction mixture filtered through celite® and concentrated *in vacuo* to afford the title compound as a pale yellow oil (84 mg, 98%).  $[\alpha]_{\text{D}}^{20} +34.2$  (*c* 1.87, CH<sub>2</sub>Cl<sub>2</sub>). All other data as previously stated.

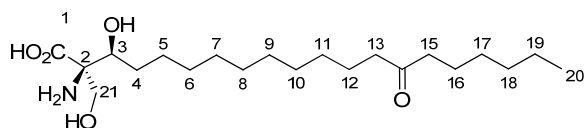
**(2*S*,3*R*)-2-Amino-3-hydroxy-2-(hydroxymethyl)-14-oxoicosanoic acid ((-)-Mycestericin G) (30)**



To a solution of (2*S*,4*S*)-3-*tert*-butoxycarbonyl)-2-*tert*-butyl-4-((*R*)-1-hydroxy-12-oxooctadecyl)oxazolidine-4-carboxylic acid *ent*-295 (47 mg, 84.6 μmol, 1.0 eq) in MeOH (1.5 mL) was added 6*N* HCl (250 μL, 1.69 mmol, 20 eq) and the reaction mixture refluxed for 18 hours. Reaction mixture was allowed to cool to room temperature and concentrated *in vacuo* to afford the crude hydrochloride salt. Residue dissolved in MeOH (2.5 mL) and neutralised to pH 5-6 with 2*N* NaOH and concentrated *in vacuo* before the residue dissolved in water (5 mL) and the white precipitate filtered to afford (-)-mycestericin G **30** (13.9 mg, 43%). Mpt: 188-190 °C (lit.<sup>50</sup> 190-191.5 °C);  $[\alpha]_{\text{D}}^{20} +13.3$  (*c* 0.3, MeOH), lit.<sup>50</sup>  $[\alpha]_{\text{D}}^{20} -6.81$  (*c* 0.106, MeOH); FTIR (film/cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 3384, 3084, 2920, 2851, 1707, 1595; <sup>1</sup>H NMR (500 MHz, MeOD)  $\delta_{\text{H}}$  0.90 (3H, t, *J* = 6.9 Hz), 1.23–1.45 (20H, m), 1.54 (4H, app. quint, *J* = 7.0 Hz), 1.58–1.70 (2H, m), 2.44 (4H, t, *J* = 7.3 Hz), 3.82 (1H, d, *J* = 11.3 Hz), 3.84 (1H, bs), 3.94 (1H, d, *J* = 11.3 Hz); <sup>13</sup>C NMR (125 MHz, MeOD)  $\delta_{\text{C}}$  13.0, 22.2, 23.5 (×2), 25.9, 28.6, 28.9, 29.1, 29.2 (×2),

29.3 ( $\times 2$ ), 31.3, 31.4, 42.1 ( $\times 2$ ), 61.1, 68.5, 70.9, 172.6, 213.0; HRMS (ESI, -ve)  $m/z$  calcd. for  $C_{21}H_{40}NO_5$  386.2906, found: 386.2913 ( $M-H$ ) $^-$ .

**(2*R*,3*S*)-2-Amino-3-hydroxy-2-(hydroxymethyl)-14-oxoicosanoic acid ((+)-Mycestericin G) (*ent*-5)**

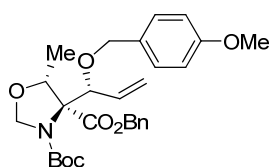


To a solution of (2*R*,4*R*)-3-*tert*-butoxycarbonyl)-2-*tert*-butyl-4-((*S*)-1-hydroxy-12-oxooctadecyl)oxazolidine-4-carboxylic acid **295** (103 mg, 0.186 mmol) in MeOH (3.0 mL) was added 6*N* HCl (620  $\mu$ L, 3.72 mmol) and the reaction mixture refluxed for 18 hours. Reaction mixture was allowed to cool to room temperature and concentrated *in vacuo* to afford the crude hydrochloride salt. Residue dissolved in MeOH (2.5 mL) and neutralised to pH 5-6 with 2*N* NaOH and concentrated *in vacuo* before the residue dissolved in water (5 mL) and the white precipitate filtered to afford crude mycestericin G. Passed through a column of amberlite IRC-76 ion exchange resin (MeOH) and purified by flash chromatography (10:3:1  $CHCl_3$ /MeOH/ $H_2O$ , bottom layer used) to afford pure mycestericin G *ent*-5 (25 mg, 35%). Mpt: 188-189  $^{\circ}C$ ;  $[\alpha]_D^{20}$  -14.0 ( $c$  1.2, MeOH). All other data as previously stated.

position	synthetic sample	isolated sample (reported) <sup>50</sup>
H20 ( $CH_3$ )	0.90 (3H, t, $J$ = 6.9 Hz)	0.90 (3H, t, $J$ = 6.6 Hz)
H5-11, H17-19 ( $CH_2$ )	1.23–1.45 (20H, m)	1.30 (20H, m)
H4	not observed, seen with neighbouring multiplet	1.36 (1H, m)
H12, H16 ( $CH_2$ )	1.54 (4H, app. quint, $J$ = 7.0 Hz)	1.54 (4H, quint, $J$ = 6.5 Hz)
H4	1.58–1.70 (2H, m)	1.62 (1H, m)
H13, H15 ( $CH_2$ )	2.44 (4H, t, $J$ = 7.3 Hz)	2.44 (4H, t, $J$ = 7.1 Hz)
H21	3.82 (1H, d, $J$ = 11.3 Hz)	3.81 (1H, $J$ = 11.1 Hz)
H3	3.84 (1H, bs)	3.83 (1H, m)
H21	3.94 (1H, d, $J$ = 11.3 Hz)	3.93 (1H, d, $J$ = 11.1 Hz)
$[\alpha]_D^{20}$	-15.0 ( $c$ 1.2, MeOH)	-6.81 ( $c$ 0.106, MeOH)

No previous  $^{13}\text{C}$  data has been reported for either the naturally isolated sample, or any synthetic sample.

**(4*S*,5*R*)- 4-Benzyl 3-*tert*-butyl 4-((*R*)-1-(4-methoxybenzyloxy)allyl)-5-methyloxazolidine-3,4-dicarboxylate (297)**

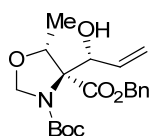


To a solution of (4*S*,5*R*)-3-*tert*-butyl 4-((*E*)-3-(4-methoxybenzyloxy)allyl) 5-methyloxazolidine-3,4-dicarboxylate **238e** (885 mg, 1.97 mmol) in THF (8.9 mL) at -78 °C was added TMSCl (752  $\mu\text{L}$ , 5.91 mmol). After 10 mins LHMDS (1M, 5.91 mL, 5.91 mmol) was added *via* syringe pump at an addition rate of 3 mL min $^{-1}$  and reaction mixture allowed to warm to room temperature after a period of 30 mins, and stirred for 18 hours. The reaction was quenched by the addition of 1N HCl and brine solution (1:1, 5 mL) and extracted with DCM (3  $\times$  15 mL), EtOAc (1  $\times$  15 mL), dried over Na $_2$ SO $_4$  and concentrated *in vacuo* to afford the crude acid. Treatment with diazomethane according to general procedure VIII and purification by flash chromatography (10:1 Pet/EtOAc) affords the methyl ester as a colourless oil (723 mg, 68%, dr >99:1).  $[\alpha]_{\text{D}}^{20}$  -30.7 (*c* 2.15, CHCl $_3$ ); FTIR (film/cm $^{-1}$ )  $\nu_{\text{max}}$ : 2979, 2935, 2868, 1738, 1699;  $^1\text{H}$  NMR (500MHz, CDCl $_3$ , 328K)  $\delta_{\text{H}}$  rotamer A 1.14 (3H, d,  $J$  = 6.4 Hz), 1.37 (9H, s), 3.81 (3H, s), 4.34 (1H, quin,  $J$  = 6.1 Hz), 4.37–4.43 (1H, m), 4.50–4.57 (1H, m), 4.70 (1H, app. d,  $J$  = 4.2 Hz), 4.73 (1H, app. d,  $J$  = 4.2 Hz), 5.10–5.39 (4H, m), 5.48 (1H, app. dd,  $J$  = 17.4, 1.8 Hz), 6.19–6.31 (1H, m), 6.86–6.92 (2H, m), 7.25 (2H, app. d,  $J$  = 8.5 Hz), 7.29–7.44 (5H, m);  $\delta_{\text{H}}$  rotamer B 1.18 (3H, d,  $J$  = 6.4 Hz), 1.42 (9H, s), 3.82 (3H, s), 4.34 (1H, quin,  $J$  = 6.1 Hz), 4.37–4.43 (1H, m), 4.50–4.57 (1H, m), 4.73 (1H, app. d,  $J$  = 4.2 Hz), 4.97 (1H, app. d,  $J$  = 4.2 Hz), 5.10–5.39 (4H, m), 5.48 (1H, app. dd,  $J$  = 17.4, 1.8 Hz), 6.19–6.31 (1H, m), 6.86–6.92 (2H, m), 7.25 (2H, app. d,  $J$  = 8.5 Hz), 7.29–7.44 (5H, m);  $^{13}\text{C}$  NMR (125MHz, CDCl $_3$ )  $\delta_{\text{C}}$  rotamer A 16.3, 28.3, 55.3, 66.7, 70.9, 72.0, 76.7, 77.9, 79.5, 80.6, 113.7, 117.2, 128.1, 128.4 ( $\times 2$ ), 129.2, 130.2, 134.4, 135.1, 151.3, 159.1, 169.9;  $\delta_{\text{C}}$  rotamer B 16.3, 28.4, 55.3, 66.8, 71.0, 72.2, 77.3, 77.9, 79.8, 81.0,



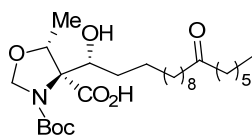
113.9, 117.5, 128.3, 128.4, 128.6, 129.3, 130.6, 134.6, 135.6, 151.8, 159.3, 170.0; HRMS (ESI, +ve)  $m/z$  calcd. for  $C_{28}H_{36}NO_7$  498.2492, found: 498.2508 ( $M+H$ )<sup>+</sup>.

**(4*R*,5*R*)-4-Benzyl 3-*tert*-butyl 4-((*R*)-1-hydroxyallyl)-5-methyloxazolidine-3,4-dicarboxylate (298)**



To a solution of (4*S*,5*R*)-4-benzyl 3-*tert*-butyl 4-((*R*)-1-(4-methoxybenzyloxy)allyl)-5-methyloxazolidine-3,4-dicarboxylate **297** (475 mg, 0.955 mmol, 1 eq) in DCM/H<sub>2</sub>O (18:1, 9.0 mL) was added DDQ (270 mg, 1.19 mmol, 1.25 eq) and stirred at room temperature for 3 hours. The precipitate formed was removed by filtration, and the filtrate was concentrated *in vacuo* and purified by flash chromatography (10:1 – 8:1 Pet/EtOAc) to afford the title compound as a colourless oil (347 mg, 96%).  $[\alpha]_D^{20} +31.5$  ( $c$  2.0, CHCl<sub>3</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 3345, 2980, 2936, 2884, 1740, 1683; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_H$  1.27 (3H, d,  $J$  = 6.4 Hz), 1.45 (9H, s), 4.06 (1H, q,  $J$  = 6.4 Hz), 4.47 (1H, app. t,  $J$  = 8.4 Hz), 4.73 (1H, d,  $J$  = 3.7 Hz), 5.06 (1H, d,  $J$  = 3.7 Hz), 5.22 (1H, d,  $J$  = 12.5 Hz), 5.26–5.39 (3H, m), 5.82 (1H, d,  $J$  = 10.3 Hz), 5.89 (1H, ddd,  $J$  = 17.3, 10.3, 7.1 Hz), 7.30–7.42 (5H, m); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_C$  15.6, 28.2, 67.4, 73.4, 74.5, 79.5, 80.3, 82.1, 118.7, 128.2, 128.3, 128.5, 135.4, 135.7, 154.3, 168.4; HRMS (ESI, +ve)  $m/z$  calcd. for  $C_{20}H_{27}NO_6Na$  400.1736, found: 400.1743 ( $M+Na$ )<sup>+</sup>.

**(4*R*,5*R*)-3-(*tert*-Butoxycarbonyl)-4-((*R*)-1-hydroxy-5-oxoheptyl)-5-methyloxazolidine-4-carboxylic acid (299)**

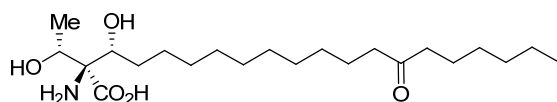


To a solution of (4*R*,5*R*)-4-benzyl 3-*tert*-butyl 4-((*R*)-1-hydroxyallyl)-5-methyloxazolidine-3,4-dicarboxylate **298** (200 mg, 0.530 mmol, 1 eq) and (*E*)-Dotriacont-16-ene-7,26-dione **289** (253 mg, 0.530 mmol, 1 eq) in DCM (1.5 mL) was

added Hoveyda-Grubbs II (16.6 mg, 26.5  $\mu\text{mol}$ , 5 mol%) and heated at reflux for 24 hours. Reaction mixture concentrated *in vacuo* and some residual impurities removed by flash chromatography (10:1 Pet/EtOAc) to afford the crude allylic alcohol as a pale yellow oil.

Allylic alcohol (123 mg, 0.204 mmol, 1.0 eq) and 10 mol% Pd/C (12 mg, 10 wt%) in EtOH (5.0 mL) was hydrogenated at atmospheric pressure for 1 hours. Reaction mixture filtered through celite® and concentrated *in vacuo*. Purified by flash chromatography (8:1 – 2:1 Pet/EtOAc) to afford the title compound as a colourless oil (88 mg, 34%, 8:1 mix of rotamers).  $[\alpha]_D^{20} +18.1$  (*c* 2.65,  $\text{CHCl}_3$ ); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 3156, 2927, 2856, 1707, 1684;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  major rotamer 0.88 (3H, t,  $J = 6.9$  Hz), 1.21–1.36 (20H, m), 1.39 (3H, d,  $J = 6.4$  Hz), 1.48 (9H, s), 1.50–1.61 (5H, m), 1.62–1.73 (1H, m), 2.38 (4H, t,  $J = 7.5$  Hz), 3.92 (1H, d,  $J = 9.6$  Hz), 4.07 (1H, q,  $J = 6.4$  Hz), 4.79 (1H, d,  $J = 3.7$  Hz), 5.06 (1H, d,  $J = 3.7$  Hz), 5.65 (1H, bs), 8.88 (1H, bs);  $\delta_{\text{H}}$  minor rotamer 0.88 (3H, t,  $J = 6.9$  Hz), 1.21–1.36 (20H, m), 1.39 (3H, d,  $J = 6.4$  Hz), 1.45 (9H, s), 1.50–1.61 (5H, m), 1.62–1.73 (1H, m), 2.38 (4H, t,  $J = 7.5$  Hz), 3.92 (1H, d,  $J = 9.6$  Hz), 4.33 (1H, q,  $J = 5.9$  Hz), 4.71 (1H, d,  $J = 3.5$  Hz), 5.37 (1H, d,  $J = 3.5$  Hz), 5.65 (1H, bs), 8.88 (1H, bs);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  mixture of rotamers 14.0, 16.0, 16.4, 22.5, 23.8, 23.9, 26.1, 27.0, 28.2, 28.3, 28.9, 29.3, 29.4 ( $\times 3$ ), 29.5 ( $\times 3$ ), 29.6 ( $\times 2$ ), 31.6, 32.2, 42.8, 71.9, 72.2, 72.8, 75.1, 77.2, 79.5, 79.9, 80.0, 82.1, 82.7, 152.5, 154.3, 172.0, 212.0; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{28}\text{H}_{51}\text{NO}_7\text{Na}$  536.3563, found: 536.3567 ( $\text{M}+\text{Na}$ ) $^+$ .

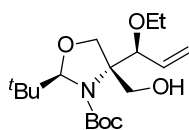
**(2*S*,3*R*)-2-Amino-3-hydroxy-2-((*R*)-1-hydroxyethyl)-14-oxoicosanoic acid (296)**



To a solution of (4*R*,5*R*)-3-(*tert*-butoxycarbonyl)-4-((*R*)-1-hydroxy-5-oxoheptyl)-5-methyloxazolidine-4-carboxylic acid **299** (53 mg, 0.103 mmol, 1.0 eq) in MeOH (1.5 mL) was added 6N HCl (350  $\mu\text{L}$ , 2.06 mmol, 20 eq) and the reaction mixture refluxed for 2 hours. Reaction mixture was allowed to cool to room temperature and concentrated *in vacuo* to afford the crude hydrochloride salt. Residue dissolved in

MeOH (2.5 mL) and neutralised to pH 5-6 with 2*N* NaOH and concentrated *in vacuo* before the residue dissolved in water (5 mL) and the white precipitate filtered. Filtrate concentrated *in vacuo* and purified by flash chromatography (10:3:1 CHCl<sub>3</sub>/MeOH/H<sub>2</sub>O; bottom layer used) to afford the title compound as a white amorphous solid (5.0 mg, 12%).  $[\alpha]_D^{20} +24.0$  (*c* 0.25, MeOH); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 3308, 2920, 2851, 1710, 1640; <sup>1</sup>H NMR (500 MHz, MeOD)  $\delta_H$  0.92 (3H, t, *J* = 7.0 Hz), 1.24 (3H, d, *J* = 6.6 Hz), 1.27–1.48 (20H, m), 1.52–1.60 (4H, m), 1.61–1.79 (2H, m), 2.46 (4H, t, *J* = 7.3 Hz), 3.14 (1H, s), 3.90 (1H, d, *J* = 10.3 Hz), 4.40 (1H, q, *J* = 6.6 Hz); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_C$  13.0, 17.2, 22.2, 23.3, 23.5 ( $\times 2$ ), 25.9, 28.6, 28.9, 29.2 ( $\times 2$ ), 29.3, 29.4, 31.4 ( $\times 2$ ), 32.0, 42.1, 65.4, 70.2, 71.1, 172.1, 213.0; HRMS (ESI, +ve) *m/z* calcd. for C<sub>22</sub>H<sub>44</sub>NO<sub>5</sub> 402.3219, found: 402.3218 (M+H)<sup>+</sup>.

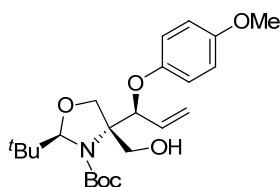
**(2*R*,4*R*)-tert-Butyl 2-tert-butyl-4-((*S*)-1-ethoxyallyl)-4-(hydroxymethyl)oxazolidine-3-carboxylate (323a)**



To a stirred solution of lithium aluminium hydride (16 mg, 0.415 mmol, 2.0 eq) in THF (0.4 mL) at 0 °C was added a solution of (2*R*,4*R*)-3-tert-butyl 4-methyl 2-tert-butyl-4-((*S*)-1-ethoxyallyl)oxazolidine-3,4-dicarboxylate **252b** (77 mg, 0.207 mmol, 1.0 eq) in THF (2.0 mL) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. Reaction mixture poured into an ice-cold solution of saturated Rochelle salt (15 mL) and EtOAc (10 mL). The biphasic mixture was stirred vigorously at room temperature for 2 hours before extracting with EtOAc (3  $\times$  25 mL). The organics were combined, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to afford the pure title compound as a colourless oil without the need for further purification (71 mg, 100%).  $[\alpha]_D^{20} +39.4$  (*c* 1.6, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 3396, 2978, 2936, 2878, 1695, 1665; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_H$  0.95 (9H, s), 1.20 (3H, t, *J* = 7.0 Hz), 1.52 (9H, s), 3.24 (1H, dq, *J* = 9.1, 7.0 Hz), 3.42 (1H, d, *J* = 8.5 Hz), 3.50 (1H, d, *J* = 11.8 Hz), 3.61 (1H, dq, *J* = 9.1, 7.0 Hz), 3.79 (1H, d, *J* = 11.8 Hz), 4.21 (1H, d, *J* = 8.5 Hz), 4.79 (1H, bs), 5.10 (1H, s), 5.35 (1H, app. dt, *J* = 10.5, 1.5 Hz), 5.50 (1H, d, *J* = 17.3 Hz), 5.80 (1H, ddd, *J* = 17.3, 10.5, 6.2 Hz); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_C$

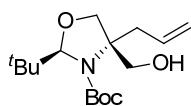
15.6, 26.6, 28.2, 38.8, 65.2, 65.9, 69.5, 70.9, 76.6, 82.1, 98.5, 118.8, 134.9, 156.5; HRMS (ESI, +ve)  $m/z$  calcd. for  $C_{18}H_{33}NO_5$  344.2437, found: 344.2424 ( $M+H$ )<sup>+</sup>.

**(2*R*,4*R*)-tert-Butyl 2-tert-butyl-4-(hydroxymethyl)-4-((*S*)-1-(4-methoxyphenoxy)allyl)oxazolidine-3-carboxylate (323b)**



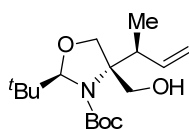
To a stirred solution of lithium aluminium hydride (16 mg, 0.428 mmol, 2.0 eq) in THF (0.4 mL) at 0 °C was added a solution of (2*R*,4*R*)-3-tert-butyl 4-methyl 2-tert-butyl-4-((*S*)-1-methoxyphenoxyallyl)oxazolidine-3,4-dicarboxylate **252g** (96 mg, 0.214 mmol, 1.0 eq) in THF (2.0 mL) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. Reaction mixture poured into an ice-cold solution of saturated Rochelle salt (15 mL) and EtOAc (10 mL). The biphasic mixture was stirred vigorously at room temperature for 2 hours before extracting with EtOAc (3 × 25 mL). The organics were combined, dried over  $MgSO_4$ , filtered and concentrated *in vacuo* to afford the pure title compound as a colourless oil without the need for further purification (80 mg, 89%).  $[\alpha]_D^{20} +59.4$  ( $c$  2.39,  $CH_2Cl_2$ ); FTIR (film/ $cm^{-1}$ )  $\nu_{max}$ : 3381, 2977, 2960, 2875, 1661;  $^1H$  NMR (500MHz,  $CDCl_3$ )  $\delta_H$  0.96 (9H, s), 1.16 (9H, s), 3.51 (1H, d,  $J = 9.0$  Hz), 3.58 (1H, t,  $J = 11.5$  Hz), 3.74 (3H, s), 3.88 (1H, d,  $J = 12.1$  Hz), 4.36 (1H, d,  $J = 9.0$  Hz), 5.20 (1H, bs), 5.38 (1H, d,  $J = 10.8$  Hz), 5.51 (1H, app. dt,  $J = 17.4, 1.6$  Hz), 5.54–5.64 (2H, m), 6.00 (1H, ddd,  $J = 17.4, 10.8, 4.2$  Hz), 6.74–6.79 (2H, m), 6.81–6.85 (2H, m);  $^{13}C$  NMR (125MHz,  $CDCl_3$ )  $\delta_C$  26.5, 27.7, 38.9, 55.7, 65.9, 69.8, 70.9, 75.7, 82.5, 98.8, 114.4, 116.5, 119.1, 133.7, 152.6, 154.0, 156.3; HRMS (ESI, +ve)  $m/z$  calcd. for  $C_{23}H_{36}NO_6$  422.2543, found: 422.2546 ( $M+H$ )<sup>+</sup>.

**(2*R*,4*R*)-tert-Butyl 4-allyl-2-tert-butyl-4-(hydroxymethyl)oxazolidine-3-carboxylate (323c)**



To a stirred solution of lithium aluminium hydride (23 mg, 0.610 mmol, 2.0 eq) in THF (0.6 mL) at 0 °C was added a solution of (2*R*,4*S*)-3-*tert*-butyl 4-methyl 4-allyl-2-*tert*-butyloxazolidine-3,4-dicarboxylate **266a** (100 mg, 0.305 mmol, 1.0 eq) in THF (2.8 mL) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. Reaction mixture poured into an ice-cold solution of saturated Rochelle salt (15 mL) and EtOAc (10 mL). The biphasic mixture was stirred vigorously at room temperature for 2 hours before extracting with EtOAc (3 × 25 mL). The organics were combined, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to afford the pure title compound as a colourless oil without the need for further purification (91 mg, 100%).  $[\alpha]_{\text{D}}^{20} +17.5$  (*c* 3.03, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 3397, 2976, 2932, 1699, 1666; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>, 328K)  $\delta_{\text{H}}$  0.95 (9H, s), 1.45 (9H, s), 2.47 (1H, dd, *J* = 14.0, 6.0 Hz), 2.84 (1H, dd, *J* = 14.0, 8.8 Hz), 3.55 (1H, app. t, *J* = 9.3 Hz), 3.75 (1H, d, *J* = 8.6 Hz), 3.82 (1H, d, *J* = 11.5 Hz), 3.96 (1H, d, *J* = 8.9 Hz), 5.05 (1H, s), 5.10–5.18 (2H, m), 5.78–5.88 (1H, m); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  26.7, 28.1, 36.2, 38.9, 66.8, 67.9, 73.4, 82.1, 97.9, 119.1, 133.1, 155.9; HRMS (ESI, +ve) *m/z* calcd. for C<sub>16</sub>H<sub>30</sub>NO<sub>4</sub> 300.2175, found: 300.2178 (M+H)<sup>+</sup>.

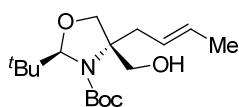
**(2*R*,4*R*)-*tert*-Butyl 4-((*S*)-but-3-en-2-yl)-2-*tert*-butyl-4-(hydroxymethyl)oxazolidine-3-carboxylate (323d)**



To a stirred solution of lithium aluminium hydride (33 mg, 0.862 mmol, 2.0 eq) in THF (0.9 mL) at 0 °C was added a solution of (2*R*,4*S*)-3-*tert*-butyl 4-methyl 4-((*S*)-but-3-en-2-yl)-2-*tert*-butyloxazolidine-3,4-dicarboxylate **266b** (147 mg, 0.431 mmol, 1.0 eq) in THF (12.5 mL) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 4 hours. Reaction mixture poured into an ice-cold solution of saturated Rochelle salt (15 mL) and EtOAc (10 mL). The biphasic mixture was stirred vigorously at room temperature for 2 hours before extracting with EtOAc (3 × 25 mL). The organics were combined, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to afford the pure title compound as a colourless oil without the need for further purification (131 mg, 98%). FTIR (film/cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 3397, 2975, 2916, 1699, 1666; <sup>1</sup>H

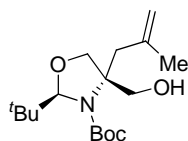
NMR (500MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  0.96 (9H, s), 0.98 (3H, d,  $J = 7.0$  Hz), 1.51 (9H, s), 3.51 (2H, bs), 3.60 (1H, d,  $J = 11.6$  Hz), 3.79 (1H, d,  $J = 11.6$  Hz), 4.01 (1H, d,  $J = 9.2$  Hz), 4.83–5.50 (1H, bs), 5.05 (1H, s), 5.13 (1H, d,  $J = 10.4$  Hz), 5.24 (1H, d,  $J = 17.3$  Hz), 5.86 (1H, ddd,  $J = 17.3, 10.4, 6.8$  Hz);  $^{13}\text{C}$  NMR (125MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  12.7, 26.7, 28.1, 35.4, 39.0, 66.5, 70.1, 70.3, 82.0, 98.2, 116.5, 139.3, 155.7; HRMS (ESI, +ve)  $m/z$  calcd. for C<sub>17</sub>H<sub>31</sub>NO<sub>4</sub>Na 336.2151, found: 336.2153 (M+Na)<sup>+</sup>.

**(2*R*,4*R*)-tert-Butyl 4-((*E*)-but-2-enyl)-2-tert-butyl-4-(hydroxymethyl)oxazolidine-3-carboxylate (323e)**



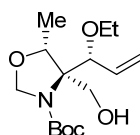
To a stirred solution of lithium aluminium hydride (130 mg, 3.42 mmol, 2.0 eq) in THF (12.5 mL) at 0 °C was added a solution of (2*R*,4*S*)-3-*tert*-butyl 4-methyl 4-((*E*)-but-2-enyl)-2-*tert*-butyloxazolidine-3,4-dicarboxylate **333a** (584 mg, 1.71 mmol, 1.0 eq) in THF (12.5 mL) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 4 hours. Reaction mixture poured into an ice-cold solution of saturated Rochelle salt (15 mL) and EtOAc (10 mL). The biphasic mixture was stirred vigorously at room temperature for 2 hours before extracting with EtOAc (3 × 25 mL). The organics were combined, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to afford the pure title compound as a colourless oil without the need for further purification (536 mg, 100%, 5:1 mix of rotamers). FTIR (film/cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 3388, 2973, 2934, 2911;  $^1\text{H}$  NMR (500MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  major rotamer 0.94 (9H, s), 1.48 (9H, s), 1.69 (3H, d,  $J = 5.9$  Hz), 2.36–2.53 (1H, m), 2.76 (1H, bs), 3.51 (1H, bs), 3.68 (1H, bs), 3.81 (1H, d,  $J = 11.0$  Hz), 3.96 (1H, d,  $J = 8.8$  Hz), 5.02 (1H, s), 5.21–5.70 (3H, m);  $\delta_{\text{H}}$  minor rotamer 0.94 (9H, s), 1.48 (9H, s), 1.69 (3H, d,  $J = 5.9$  Hz), 2.36–2.53 (1H, m), 2.88 (1H, bs), 3.51 (1H, bs), 3.68 (1H, bs), 3.81 (1H, d,  $J = 11.0$  Hz), 3.89 (1H, d,  $J = 8.8$  Hz), 5.09 (1H, s), 5.21–5.70 (3H, m);  $^{13}\text{C}$  NMR (125MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  18.1, 26.7, 28.1, 34.9, 38.9, 66.7, 68.0, 73.5, 82.0, 97.9, 125.4, 129.8, 156.0; HRMS (ESI, +ve)  $m/z$  calcd. for C<sub>17</sub>H<sub>31</sub>NO<sub>4</sub>Na 336.2151, found: 336.2157 (M+Na)<sup>+</sup>.

**(2*R*,4*R*)-tert-Butyl 2-tert-butyl-4-(hydroxymethyl)-4-(2-methylallyl)oxazolidine-3-carboxylate (323f)**



To a stirred solution of lithium aluminium hydride in THF (2.4M, 560  $\mu$ L, 1.32 mmol, 2.0 eq) at 0 °C was added a solution of (2*R*,4*S*)-3-*tert*-butyl 4-methyl 2-*tert*-butyl-4-(2-methylallyl)oxazolidine-3,4-dicarboxylate **333b** (226 mg, 0.662 mmol, 1.0 eq) in THF (6.0 mL) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 1 hours. Reaction mixture poured into an ice-cold solution of saturated Rochelle salt (15 mL) and EtOAc (10 mL). The biphasic mixture was stirred vigorously at room temperature for 2 hours before extracting with EtOAc (3  $\times$  25 mL). The organics were combined, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to afford the pure title compound as a colourless oil without the need for further purification (169 mg, 82%).  $[\alpha]_D^{20}$  +25.5 (*c* 2.2, CHCl<sub>3</sub>); FTIR (film/cm-1)  $\nu_{\max}$ : 3382, 2969, 2928, 1697, 1665; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_H$  0.95 (9H, s), 1.48 (9H, s), 1.81 (3H, s), 2.39 (1H, d, *J* = 13.8 Hz), 2.87 (1H, app. d, *J* = 8.1 Hz), 3.51 (1H, bs), 3.65 (1H, bs), 3.84 (1H, d, *J* = 11.3 Hz), 4.09 (1H, d, *J* = 9.0 Hz), 4.80 (1H, s), 4.93 (1H, s), 5.03 (1H, bs), 5.40 (1H, bs); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_C$  23.6, 26.9, 28.2, 38.6, 39.0, 67.7, 67.9, 72.4, 82.2, 97.6, 116.1, 141.8, 155.8; HRMS (ESI, +ve) *m/z* calcd. for C<sub>17</sub>H<sub>32</sub>NO<sub>4</sub> 314.2331, found: 314.2323 (M+H)<sup>+</sup>.

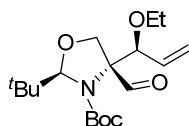
**(4*S*,5*R*)-tert-Butyl 4-((*R*)-1-ethoxyallyl)-4-(hydroxymethyl)-5-methyloxazolidine-3-carboxylate (324)**



To a stirred solution of lithium aluminium hydride (57 mg, 1.51 mmol, 2.0 eq) in THF (1.5 mL) at 0 °C was added a solution of (4*S*,5*R*)-3-*tert*-butyl 4-methyl 4-((*R*)-1-ethoxyallyl)-5-methyloxazolidine-3,4-dicarboxylate **239d** (249 mg, 0.756 mmol, 1.0 eq)

in THF (7.0 mL) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. Reaction mixture poured into an ice-cold solution of saturated Rochelle salt (15 mL) and EtOAc (10 mL). The biphasic mixture was stirred vigorously at room temperature for 2 hours before extracting with EtOAc (3 × 25 mL). The organics were combined, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to afford the pure title compound as a colourless oil without the need for further purification (192 mg, 84%, 10:1 mix of rotamers).  $[\alpha]_D^{20}$  -36.2 (*c* 2.35, CHCl<sub>3</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 3378, 2976, 2931, 2875, 1673; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  major rotamer 1.14 (3H, t, *J* = 7.0 Hz), 1.20 (3H, d, *J* = 6.6 Hz), 1.47 (9H, s), 3.28–3.38 (1H, m), 3.49–3.62 (1H, m), 3.75 (2H, bs), 4.38 (1H, q, *J* = 6.6 Hz), 4.61 (1H, d, *J* = 3.9 Hz), 4.71 (1H, bs), 4.80 (1H, d, *J* = 6.3 Hz), 4.91 (1H, d, *J* = 3.9 Hz), 5.29 (1H, d, *J* = 10.6 Hz), 5.42 (1H, d, *J* = 17.3 Hz), 5.75 (1H, ddd, *J* = 17.3, 10.6, 6.5 Hz);  $\delta_{\text{H}}$  minor rotamer 1.14 (3H, t, *J* = 7.0 Hz), 1.20 (3H, d, *J* = 6.6 Hz), 1.50 (9H, s), 3.28–3.38 (1H, m), 3.49–3.62 (1H, m), 3.75 (2H, bs), 4.46 (1H, q, *J* = 6.6 Hz), 4.53 (1H, d, *J* = 3.9 Hz), 4.71 (1H, bs), 4.80 (1H, d, *J* = 6.3 Hz), 4.85 (1H, d, *J* = 3.9 Hz), 5.29 (1H, d, *J* = 10.6 Hz), 5.42 (1H, d, *J* = 17.3 Hz), 5.53 (1H, ddd, *J* = 17.3, 10.6, 6.5 Hz); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  major rotamer 15.4, 15.6, 28.3, 64.6, 64.8, 68.2, 76.3, 76.8, 79.2, 81.0, 118.5, 134.2, 154.5;  $\delta_{\text{C}}$  minor rotamer 15.3, 16.9, 29.6, 59.9, 63.2, 66.3, 76.3, 77.2, 82.5, 85.7, 119.4, 133.7, 154.5; HRMS (ESI, +ve) *m/z* calcd. for C<sub>15</sub>H<sub>27</sub>NO<sub>5</sub>Na 324.1787, found: 324.1768 (M+Na)<sup>+</sup>.

**(2*R*,4*R*)-*tert*-Butyl 2-*tert*-butyl-4-((*S*)-1-ethoxyallyl)-4-formyloxazolidine-3-carboxylate (325a)**

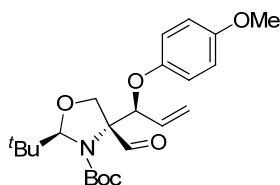


DMSO (78  $\mu$ L, 1.10 mmol, 5.4 eq) in DCM (400  $\mu$ L) was added dropwise to a solution of oxalyl chloride (47  $\mu$ L, 0.551 mmol, 2.7 eq) in DCM (1.0 mL) at -78 °C and stirred for 30 minutes. (2*R*,4*R*)-*tert*-butyl 2-*tert*-butyl-4-((*S*)-1-ethoxyallyl)-4-(hydroxymethyl)oxazolidine-3-carboxylate **323a** (70 mg, 0.204 mmol, 1 eq) in DCM (1.2 mL) was added dropwise to the reaction mixture and stirred for a further 15



minutes.  $\text{NEt}_3$  (182  $\mu\text{L}$ , 1.31 mmol, 6.4 eq) in DCM (400  $\mu\text{L}$ ) was added dropwise and the reaction mixture allowed to warm to room temperature and stirred for 2 hours. Reaction mixture diluted with DCM (15 mL) and washed with water ( $3 \times 10$  mL) and  $\text{NaHCO}_3$  (sat) ( $3 \times 10$  mL). The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo* to afford the pure title compound as a colourless oil without the need for further purification (54 mg, 78%).  $[\alpha]_{\text{D}}^{20}$  -15.2 (*c* 1.05,  $\text{CH}_2\text{Cl}_2$ ); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2978, 2937, 2906, 2876, 1724, 1695;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  0.94 (9H, s), 1.20 (3H, t,  $J = 7.0$  Hz), 1.51 (9H, s), 3.30 (1H, app. quin.,  $J = 7.0$  Hz), 3.61 (1H, app. t,  $J = 7.0$  Hz), 4.06–4.23 (2H, m), 4.87 (1H, bs), 5.16 (1H, s), 5.34 (1H, d,  $J = 10.6$  Hz), 5.38 (1H, d,  $J = 17.3$  Hz), 5.71 (1H, bs), 9.73 (1H, s);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  15.4, 26.4, 28.2, 38.8, 64.8, 67.3, 74.8, 78.6, 81.6, 97.9, 119.4, 134.2, 154.2, 197.3; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{18}\text{H}_{31}\text{NO}_5\text{Na}$  364.2094, found: 364.2113 ( $\text{M}+\text{Na}$ ) $^+$ .

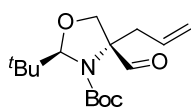
**(2*R*,4*R*)-tert-Butyl 2-tert-butyl-4-formyl-4-((*S*)-1-(4-methoxyphenoxy)allyl)oxazolidine-3-carboxylate (325b)**



DMSO (64  $\mu\text{L}$ , 0.897 mmol, 5.4 eq) in DCM (400  $\mu\text{L}$ ) was added dropwise to a solution of oxalyl chloride (39  $\mu\text{L}$ , 0.448 mmol, 2.7 eq) in DCM (1.0 mL) at  $-78$   $^{\circ}\text{C}$  and stirred for 30 minutes. (2*R*,4*R*)-tert-butyl 2-tert-butyl-4-(hydroxymethyl)-4-((*S*)-1-(4-methoxyphenoxy)allyl)oxazolidine-3-carboxylate **323b** (70 mg, 0.166 mmol, 1 eq) in DCM (1.2 mL) was added dropwise to the reaction mixture and stirred for a further 15 minutes.  $\text{NEt}_3$  (148  $\mu\text{L}$ , 1.31 mmol, 6.4 eq) in DCM (400  $\mu\text{L}$ ) was added dropwise and the reaction mixture allowed to warm to room temperature and stirred for 2 hours. Reaction mixture diluted with DCM (15 mL) and washed with water ( $3 \times 10$  mL) and  $\text{NaHCO}_3$  (sat) ( $3 \times 10$  mL). The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo* to afford the pure title compound as a colourless oil without the need for further purification (55 mg, 80%).  $[\alpha]_{\text{D}}^{20}$  +46.5 (*c* 2.0,  $\text{CH}_2\text{Cl}_2$ ); FTIR (film/ $\text{cm}^{-1}$

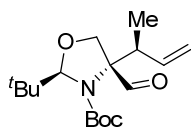
1)  $\nu_{\max}$ : 2977, 2939, 2912, 2876, 1726, 1694;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ , 328K)  $\delta_{\text{H}}$  1.01 (9H, s), 1.20 (9H, s), 3.75 (3H, s), 4.19 (1H, d,  $J = 9.2$  Hz), 4.37 (1H, d,  $J = 9.2$  Hz), 5.28–5.44 (3H, m), 5.60 (1H, bs), 5.95 (1H, ddd,  $J = 16.2, 10.8, 4.2$  Hz), 6.78 (2H, app. d,  $J = 9.2$  Hz), 6.86 (2H, app. d,  $J = 9.2$  Hz), 9.80 (1H, s);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ , 328K)  $\delta_{\text{C}}$  26.4, 27.8, 38.9, 55.7, 67.8, 74.7, 77.1, 82.0, 98.4, 114.6, 116.8, 119.3, 133.5, 152.1, 153.7, 154.5, 196.8; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{23}\text{H}_{33}\text{NO}_6\text{Na}$  442.2200, found: 442.2219 ( $\text{M}+\text{Na}$ ) $^+$ .

**(2*R*,4*S*)-*tert*-Butyl 4-allyl-2-*tert*-butyl-4-formyloxazolidine-3-carboxylate (325c)**



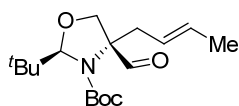
DMSO (110  $\mu\text{L}$ , 1.55 mmol, 5.4 eq) in DCM (400  $\mu\text{L}$ ) was added dropwise to a solution of oxalyl chloride (67  $\mu\text{L}$ , 0.776 mmol, 2.7 eq) in DCM (1.0 mL) at  $-78$   $^{\circ}\text{C}$  and stirred for 30 minutes. (2*R*,4*R*)-*tert*-butyl 4-allyl-2-*tert*-butyl-4-(hydroxymethyl)oxazolidine-3-carboxylate **323c** (86 mg, 0.287 mmol, 1 eq) in DCM (1.2 mL) was added dropwise to the reaction mixture and stirred for a further 15 minutes.  $\text{NEt}_3$  (257  $\mu\text{L}$ , 1.84 mmol, 6.4 eq) in DCM (400  $\mu\text{L}$ ) was added dropwise and the reaction mixture allowed to warm to room temperature and stirred for 2 hours. Reaction mixture diluted with DCM (15 mL) and washed with water ( $3 \times 10$  mL) and  $\text{NaHCO}_3$  (sat) ( $3 \times 10$  mL). The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo* to afford the pure title compound as a colourless oil without the need for further purification (64 mg, 75%).  $[\alpha]_{\text{D}}^{20} +36.5$  ( $c$  2.0,  $\text{CH}_2\text{Cl}_2$ ); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\max}$ : 2977, 2935, 2875, 1719, 1697;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  0.97 (9H, s), 1.45 (9H, s), 2.56 (1H, app. d,  $J = 9.0$  Hz), 2.90 (1H, s), 3.93 (1H, d,  $J = 9.1$  Hz), 4.14 (1H, d,  $J = 9.1$  Hz), 5.11 (1H, s), 5.14–5.20 (2H, m), 5.75–5.87 (1H, m), 9.75 (1H, s);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  26.5, 28.1, 36.2, 39.3, 71.3, 71.9, 81.7, 97.7, 119.9, 131.4, 153.6, 199.2; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{16}\text{H}_{27}\text{NO}_4\text{Na}$  320.1838, found: 320.1835 ( $\text{M}+\text{Na}$ ) $^+$ .

**(2*R*,4*S*)-*tert*-Butyl 4-((*S*)-but-3-en-2-yl)-2-*tert*-butyl-4-formyloxazolidine-3-carboxylate (325d)**



DMSO (98  $\mu$ L, 1.38 mmol, 5.4 eq) in DCM (400  $\mu$ L) was added dropwise to a solution of oxalyl chloride (59  $\mu$ L, 0.689 mmol, 2.7 eq) in DCM (1.0 mL) at -78  $^{\circ}$ C and stirred for 30 minutes. (2*R*,4*R*)-*tert*-butyl 4-((*S*)-but-3-en-2-yl)-2-*tert*-butyl-4-(hydroxymethyl)oxazolidine-3-carboxylate **323d** (80 mg, 0.255 mmol, 1 eq) in DCM (1.2 mL) was added dropwise to the reaction mixture and stirred for a further 15 minutes. NEt<sub>3</sub> (228  $\mu$ L, 1.63 mmol, 6.4 eq) in DCM (400  $\mu$ L) was added dropwise and the reaction mixture allowed to warm to room temperature and stirred for 2 hours. Reaction mixture diluted with DCM (15 mL) and washed with water (3  $\times$  10 mL) and NaHCO<sub>3</sub> (sat) (3  $\times$  10 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo* to afford the pure title compound as a colourless oil without the need for further purification (65 mg, 82%). [ $\alpha$ ]<sub>D</sub><sup>20</sup> -60.5 (*c* 2.0, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 2976, 2913, 2871, 1713, 1697; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  0.93 (9H, s), 1.03 (3H, d, *J* = 6.9 Hz), 1.49 (9H, s), 3.59 (1H, bs) 3.99 (1H, d, *J* = 9.4 Hz), 4.21 (1H, d, *J* = 9.4 Hz), 5.11–5.16 (2H, m), 5.17 (1H, s), 5.72 (1H, bs), 9.75 (1H, s); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  12.4, 26.4, 28.1, 36.9, 39.2, 68.2, 73.0, 81.7, 97.7, 117.5, 137.9, 153.6, 198.3; HRMS (ESI, +ve) *m/z* calcd. for C<sub>17</sub>H<sub>29</sub>NO<sub>4</sub>Na 334.1994, found: 334.1982 (M+Na)<sup>+</sup>.

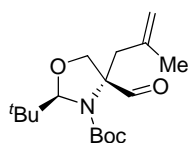
**(2*R*,4*S*)-*tert*-Butyl 4-((*E*)-but-2-enyl)-2-*tert*-butyl-4-formyloxazolidine-3-carboxylate (325e)**



DMSO (656  $\mu$ L, 9.23 mmol, 5.4 eq) in DCM (2.67 mL) was added dropwise to a solution of oxalyl chloride (397  $\mu$ L, 4.62 mmol, 2.7 eq) in DCM (6.67 mL) at -78  $^{\circ}$ C

and stirred for 30 minutes. (2*R*,4*R*)-*tert*-butyl 4-((*E*)-but-2-enyl)-2-*tert*-butyl-4-(hydroxymethyl)oxazolidine-3-carboxylate **323e** (536 mg, 1.71 mmol, 1 eq) in DCM (8.0 mL) was added dropwise to the reaction mixture and stirred for a further 15 minutes. NEt<sub>3</sub> (1.53 mL, 10.9 mmol, 6.4 eq) in DCM (2.67 mL) was added dropwise and the reaction mixture allowed to warm to room temperature and stirred for 2 hours. Reaction mixture diluted with DCM (25 mL) and washed with water (3 × 20 mL) and NaHCO<sub>3</sub> (sat) (3 × 20 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo* to afford the pure title compound as a colourless oil without the need for further purification (434 mg, 81%, 6:1 mix of rotamers). FTIR (film/cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 2973, 2934, 2875, 1718, 1698; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  major rotamer 0.98 (9H, s), 1.48 (9H, s), 1.70 (3H, app. dq, *J* = 6.4, 1.2 Hz), 2.51 (1H, app. d, *J* = 8.7 Hz), 2.85 (1H, bs), 3.94 (1H, d, *J* = 9.0 Hz), 4.15 (1H, d, *J* = 9.0 Hz), 5.11 (1H, s), 5.38–5.47 (1H, m), 5.55–5.64 (1H, m), 9.79 (1H, s);  $\delta_{\text{H}}$  minor rotamer 0.99 (9H, s), 1.47 (9H, s), 1.66 (3H, app. dq, *J* = 6.4, 1.2 Hz), 2.51 (1H, app. d, *J* = 8.7 Hz), 2.85 (1H, bs), 3.88 (1H, d, *J* = 9.0 Hz), 4.15 (1H, d, *J* = 9.0 Hz), 5.18 (1H, s), 5.38–5.47 (1H, m), 5.66–5.73 (1H, m), 9.79 (1H, s); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  13.1, 18.2, 26.5, 28.1, 39.3, 71.5, 81.6, 97.7, 122.6, 123.5, 130.6, 153.7, 200.0; HRMS (ESI, +ve) *m/z* calcd. for C<sub>17</sub>H<sub>29</sub>NO<sub>4</sub>Na 334.1994, found: 334.1996 (M+Na)<sup>+</sup>.

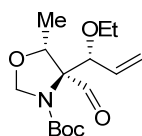
**(2*R*,4*S*)-*tert*-Butyl 2-*tert*-butyl-4-formyl-4-(2-methylallyl)oxazolidine-3-carboxylate (325f)**



DMSO (202  $\mu$ L, 2.84 mmol, 5.4 eq) in DCM (800  $\mu$ L) was added dropwise to a solution of oxalyl chloride (122  $\mu$ L, 1.42 mmol, 2.7 eq) in DCM (2.0 mL) at -78 °C and stirred for 30 minutes. (2*R*,4*R*)-*tert*-butyl 2-*tert*-butyl-4-(hydroxymethyl)-4-(2-methylallyl)oxazolidine-3-carboxylate **323f** (165 mg, 0.526 mmol, 1 eq) in DCM (2.4 mL) was added dropwise to the reaction mixture and stirred for a further 15 minutes. NEt<sub>3</sub> (470  $\mu$ L, 3.37 mmol, 6.4 eq) in DCM (800  $\mu$ L) was added dropwise and the reaction mixture allowed to warm to room temperature and stirred for 2 hours. Reaction

mixture diluted with DCM (25 mL) and washed with water ( $3 \times 20$  mL) and  $\text{NaHCO}_3$  (sat) ( $3 \times 20$  mL). The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo* to afford the pure title compound as a colourless oil without the need for further purification (116 mg, 71%).  $[\alpha]_{\text{D}}^{20} +37.7$  ( $c$  2.15,  $\text{CHCl}_3$ ); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2976, 2936, 2875, 1717, 1695;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  0.98 (9H, s), 1.46 (9H, s), 1.78 (3H, s), 2.54 (1H, d,  $J = 14.2$  Hz), 2.87 (1H, bs), 4.01 (1H, d,  $J = 9.3$  Hz), 4.08 (1H, d,  $J = 9.3$  Hz), 4.49 (1H, s), 4.95 (1H, s), 5.11 (1H, s), 9.74 (1H, s);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  23.5, 26.7, 28.1, 38.4, 39.3, 70.1, 71.9, 81.8, 97.4, 116.4, 140.4, 153.4, 199.2; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{17}\text{H}_{29}\text{NO}_4\text{Na}$  334.1994, found: 334.1987 ( $\text{M}+\text{Na}$ ) $^+$ .

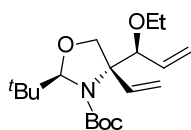
**(4*S*,5*R*)-*tert*-Butyl 4-((*R*)-1-ethoxyallyl)-4-(hydroxymethyl)-5-methyloxazolidine-3-carboxylate (326)**



DMSO (219  $\mu\text{L}$ , 3.08 mmol, 5.4 eq) in DCM (800  $\mu\text{L}$ ) was added dropwise to a solution of oxalyl chloride (132  $\mu\text{L}$ , 1.54 mmol, 2.7 eq) in DCM (2.0 mL) at  $-78^\circ\text{C}$  and stirred for 30 minutes. (4*S*,5*R*)-*tert*-butyl 4-((*R*)-1-ethoxyallyl)-4-(hydroxymethyl)-5-methyloxazolidine-3-carboxylate **324** (172 mg, 0.571 mmol, 1 eq) in DCM (2.4 mL) was added dropwise to the reaction mixture and stirred for a further 15 minutes.  $\text{NEt}_3$  (510  $\mu\text{L}$ , 3.65 mmol, 6.4 eq) in DCM (800  $\mu\text{L}$ ) was added dropwise and the reaction mixture allowed to warm to room temperature and stirred for 2 hours. Reaction mixture diluted with DCM (25 mL) and washed with water ( $3 \times 20$  mL) and  $\text{NaHCO}_3$  (sat) ( $3 \times 20$  mL). The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo* to afford the pure title compound as a colourless oil without the need for further purification (143 mg, 84%, 4:3 mix of rotamers). FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2977, 2933, 2871, 1736, 1699;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  major rotamer 1.16 (3H, t,  $J = 6.9$  Hz), 1.24 (3H, d,  $J = 4.4$  Hz), 1.48 (9H, s), 3.39 (1H, q,  $J = 7.1$  Hz), 3.57–3.66 (1H, m), 4.31–4.39 (1H, m), 4.68 (1H, d,  $J = 4.3$  Hz), 4.71 (1H, d,  $J = 3.9$  Hz), 5.17–5.44 (3H, m), 6.00–6.13 (1H, m), 9.56 (1H, s);  $\delta_{\text{H}}$  minor rotamer 1.18 (3H, t,  $J = 6.9$  Hz), 1.23 (3H, d,  $J$

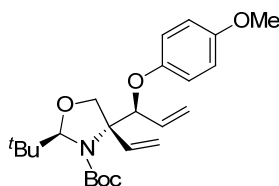
= 4.4 Hz), 1.44 (9H, s), 3.37 (1H, q,  $J = 7.1$  Hz), 3.57–3.66 (1H, m), 4.31–4.39 (1H, m), 4.42 (1H, d,  $J = 4.3$  Hz), 4.76 (1H, d,  $J = 3.9$  Hz), 5.17–5.44 (3H, m), 6.00–6.13 (1H, m), 9.49 (1H, s);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  major rotamer 15.4, 16.1, 28.3, 65.4, 72.6, 76.0, 78.4, 79.7, 81.0, 117.1, 134.3, 152.0, 199.4;  $\delta_{\text{C}}$  minor rotamer 15.4, 16.0, 28.2, 65.7, 72.5, 77.4, 79.6, 79.9, 81.7, 117.2, 134.2, 151.3, 198.8; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{15}\text{H}_{25}\text{NO}_5\text{Na}$  322.1630, found: 322.1614 ( $\text{M}+\text{Na}$ ) $^+$ .

**(2*R*,4*R*)-tert-Butyl 2-tert-butyl-4-((*S*)-1-ethoxyallyl)-4-vinyloxazolidine-3-carboxylate (327a)**



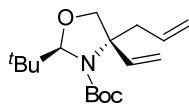
To a solution of methyltriphenylphosphonium bromide (22 mg, 61.5  $\mu\text{mol}$ , 1.5 eq) in THF (0.5 mL) at 0  $^\circ\text{C}$  was added *n*-butyl lithium (1.6M in hexane, 38  $\mu\text{L}$ , 61.5  $\mu\text{mol}$ , 1.5 eq) and the solution turned a dark yellow. After 15 minutes a solution of (2*R*,4*R*)-tert-butyl 2-tert-butyl-4-((*S*)-1-ethoxyallyl)-4-formyloxazolidine-3-carboxylate **325a** (14 mg, 41.0  $\mu\text{mol}$ , 1 eq) in THF (0.5 mL) was added and stirred at reflux for 16 hours. The reaction mixture was allowed to cool to room temperature before concentrated *in vacuo* and purified by flash chromatography (20:1 Pet/EtOAc) to afford the title compound as a colourless oil (12.1 mg, 87%).  $[\alpha]_{\text{D}}^{20}$  -19.1 ( $c$  0.47,  $\text{CH}_2\text{Cl}_2$ ); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2976, 2932, 2905, 2875, 1694;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  0.94 (9H, s), 1.19 (3H, t,  $J = 7.0$  Hz), 1.51 (9H, s), 3.28 (1H, bs), 3.56 (1H, bs), 3.94 (1H, d,  $J = 8.6$  Hz), 4.29 (1H, d,  $J = 8.6$  Hz), 4.76 (1H, bs), 5.09–5.36 (5H, m), 5.70 (1H, ddd,  $J = 17.0, 10.7, 6.5$  Hz), 6.10 (1H, bs);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  15.4, 26.7, 28.2, 38.8, 64.4, 70.2, 71.0, 78.9, 80.4, 97.9, 115.9, 118.9, 135.1, 137.5, 154.3; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{19}\text{H}_{34}\text{NO}_4$  340.2488, found: 340.2485 ( $\text{M}+\text{H}$ ) $^+$ .

**(2*R*,4*R*)-*tert*-Butyl 2-*tert*-butyl-4-((*S*)-1-(4-methoxyphenoxy)allyl)-4-vinyloxazolidine-3-carboxylate (327b)**



To a solution of methyltriphenylphosphonium bromide (60 mg, 0.168 mmol, 1.5 eq) in THF (1.5 mL) at 0 °C was added *n*-butyl lithium (1.6M in hexane, 105  $\mu$ L, 0.168 mmol, 1.5 eq) and the reaction turned a dark yellow. After 15 minutes a solution of (2*R*,4*R*)-*tert*-butyl 2-*tert*-butyl-4-((*S*)-1-(4-methoxyphenoxy)allyl)-4-formyloxazolidine-3-carboxylate **325b** (47 mg, 0.112 mmol, 1 eq) in THF (1.5 mL) was added and stirred at reflux for 16 hours. The reaction mixture was allowed to cool to room temperature before concentrated *in vacuo* and purified by flash chromatography (20:1 Pet/EtOAc) to afford the title compound as a colourless oil (34 mg, 74%).  $[\alpha]_D^{20} +10.8$  (*c* 0.74, CHCl<sub>3</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2975, 2934, 2906, 2875, 1695; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>, 328K)  $\delta_H$  0.98 (9H, s), 1.20 (9H, s), 3.74 (3H, s), 4.07 (1H, d, *J* = 8.7 Hz), 4.46 (1H, d, *J* = 8.7 Hz), 5.24–5.40 (5H, m), 4.58 (1H, bs), 5.88 (1H, ddd, *J* = 16.1, 10.8, 4.7 Hz), 6.13–6.31 (1H, m), 6.73–6.79 (2H, m), 6.81–6.86 (2H, m); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>, 328K)  $\delta_C$  26.7, 27.9, 38.8, 55.8, 69.9, 71.5, 77.1, 80.7, 98.4, 114.5, 116.6, 116.8, 119.1, 133.9, 137.3, 152.4, 153.9, 154.1; HRMS (ESI, +ve) *m/z* calcd. for C<sub>24</sub>H<sub>35</sub>NO<sub>5</sub> 417.2515, found: 417.2519 (M+H)<sup>+</sup>.

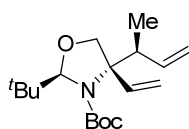
**(2*R*,4*R*)-*tert*-Butyl 4-allyl-2-*tert*-butyl-4-vinyloxazolidine-3-carboxylate (327c)**



To a solution of methyltriphenylphosphonium bromide (106 mg, 0.298 mmol, 1.5 eq) in THF (1.5 mL) at 0 °C was added *n*-butyl lithium (1.6M in hexane, 186  $\mu$ L, 0.298 mmol, 1.5 eq) and the reaction turned a dark yellow. After 15 minutes a solution of (2*R*,4*S*)-*tert*-butyl 4-allyl-2-*tert*-butyl-4-formyloxazolidine-3-carboxylate **325c** (59 mg, 0.198

mmol, 1 eq) in THF (1.5 mL) was added and stirred at reflux for 16 hours. The reaction mixture was allowed to cool to room temperature before concentrated *in vacuo* and purified by flash chromatography (20:1 Pet/EtOAc) to afford the title compound as a colourless oil (45 mg, 78%).  $[\alpha]_{\text{D}}^{20} +12.4$  (*c* 2.25, CHCl<sub>3</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 2976, 2909, 2872, 1699; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  0.95 (9H, s), 1.46 (9H, s), 2.39 (1H, dd, *J* = 13.9, 6.1 Hz), 3.09 (1H, bs), 4.00 (1H, d, *J* = 8.8 Hz), 4.07 (1H, d, *J* = 8.8 Hz), 5.06–5.20 (5H, m), 5.77–5.87 (1H, m), 6.18 (1H, bs); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  26.7, 28.3, 39.1, 40.2, 66.6, 76.4, 80.4, 97.8, 113.9, 118.8, 133.0, 140.7, 154.3; HRMS (ESI, +ve) *m/z* calcd. for C<sub>17</sub>H<sub>29</sub>NO<sub>3</sub>Na 318.2045, found: 318.2042 (M+Na)<sup>+</sup>.

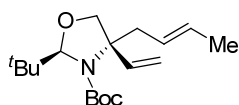
**(2*R*,4*S*)-*tert*-Butyl 4-((*S*)-but-3-en-2-yl)-2-*tert*-butyl-4-vinyloxazolidine-3-carboxylate (327d)**



To a solution of methyltriphenylphosphonium bromide (112 mg, 0.314 mmol, 1.5 eq) in THF (1.5 mL) at 0 °C was added *n*-butyl lithium (1.6M in hexane, 196  $\mu$ L, 0.314 mmol, 1.5 eq) and the reaction turned a dark yellow. After 15 minutes a solution of (2*R*,4*S*)-*tert*-butyl 4-((*S*)-but-3-en-2-yl)-2-*tert*-butyl-4-formyloxazolidine-3-carboxylate **325d** (65 mg, 0.209 mmol, 1 eq) in THF (1.5 mL) was added and stirred at reflux for 18 hours. The reaction mixture was allowed to cool to room temperature before concentrated *in vacuo* and purified by flash chromatography (20:1 Pet/EtOAc) to afford the title compound as a colourless oil (44 mg, 69%).  $[\alpha]_{\text{D}}^{20} -52.6$  (*c* 1.35, CH<sub>2</sub>Cl<sub>2</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 2975, 2936, 2875, 1698; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>, 328K)  $\delta_{\text{H}}$  0.96 (9H, s), 1.01 (3H, d, *J* = 6.9 Hz), 1.51 (9H, s), 3.39 (1H, bs), 4.02 (1H, d, *J* = 8.8 Hz), 4.08 (1H, d, *J* = 8.8 Hz), 5.03–5.13 (3H, m), 5.15–5.21 (2H, m), 5.79 (1H, ddd, *J* = 17.2, 10.5, 6.5 Hz), 6.20–6.33 (1H, m); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>, 328K)  $\delta_{\text{C}}$  13.1, 26.7, 28.3, 39.1, 40.6, 69.1, 71.6, 80.3, 97.9, 114.3, 116.1, 139.2, 139.9, 154.0; HRMS (ESI, +ve) *m/z* calcd. for C<sub>18</sub>H<sub>31</sub>NO<sub>3</sub>Na 332.2202, found: 332.2203 (M+Na)<sup>+</sup>.

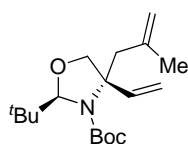


**(2*R*,4*R*)-*tert*-Butyl 4-((*E*)-but-2-enyl)-2-*tert*-butyl-4-vinyloxazolidine-3-carboxylate (327e)**



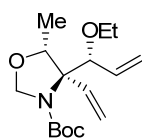
To a solution of methyltriphenylphosphonium bromide (629 mg, 1.76 mmol, 1.5 eq) in THF (7.5 mL) at 0 °C was added *n*-butyl lithium (1.6M in hexane, 1.10 mL, 1.76 mmol, 1.5 eq) and the reaction turned a dark yellow. After 15 minutes a solution of (2*R*,4*S*)-*tert*-butyl 4-((*E*)-but-2-enyl)-2-*tert*-butyl-4-formyloxazolidine-3-carboxylate **325e** (365 mg, 1.17 mmol, 1 eq) in THF (7.5 mL) was added and stirred at reflux for 3 hours. The reaction mixture was allowed to cool to room temperature before concentrated *in vacuo* and purified by flash chromatography (20:1 Pet/EtOAc) to afford the title compound as a colourless oil (267 mg, 74%, 7:1 mix of rotamers).  $[\alpha]_D^{20} +30.7$  (*c* 1.4, CHCl<sub>3</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2975, 2937, 2908, 2872, 1699; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  major rotamer 0.93 (9H, s), 1.44 (9H, s), 1.66 (3H, d, *J* = 6.6 Hz), 2.27–2.37 (1H, m), 2.95 (1H, bs), 3.97 (1H, d, *J* = 8.8 Hz), 4.03 (1H, dd, *J* = 8.8, 1.2 Hz), 5.01–5.18 (3H, m), 5.35–5.45 (1H, m), 5.48–5.57 (1H, m), 6.16 (1H, bs);  $\delta_{\text{H}}$  minor rotamer 0.94 (9H, s), 1.44 (9H, s), 1.63 (3H, d, *J* = 6.6 Hz), 2.27–2.37 (1H, m), 2.95 (1H, bs), 3.92 (1H, d, *J* = 8.8 Hz), 4.03 (1H, dd, *J* = 8.8, 1.2 Hz), 5.01–5.18 (3H, m), 5.35–5.45 (1H, m), 5.57–5.65 (1H, m), 6.16 (1H, bs); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  major rotamer 18.1, 26.7, 28.3, 39.1, 39.7, 66.7, 76.5, 80.2, 97.7, 113.7, 125.2, 129.4, 140.8, 154.2;  $\delta_{\text{C}}$  minor rotamer 13.1, 26.7, 28.3, 39.1, 39.7, 66.7, 76.5, 80.3, 97.7, 113.8, 124.5, 127.1, 140.6, 154.2; HRMS (ESI, +ve) *m/z* calcd. for C<sub>18</sub>H<sub>31</sub>NO<sub>3</sub>Na 332.2202, found: 332.2209 (M+Na)<sup>+</sup>.

**(2*R*,4*R*)-*tert*-Butyl 2-*tert*-butyl-4-(2-methylallyl)-4-vinyloxazolidine-3-carboxylate (327f)**



To a solution of methyltriphenylphosphonium bromide (198 mg, 0.554 mmol, 1.5 eq) in THF (3.0 mL) at 0 °C was added *n*-butyl lithium (1.6M in hexane, 346  $\mu$ L, 0.554 mmol, 1.5 eq) and the reaction turned a dark yellow. After 15 minutes a solution of (2*R*,4*S*)-*tert*-butyl 2-*tert*-butyl-4-formyl-4-(2-methylallyl)oxazolidine-3-carboxylate **325f** (115 mg, 0.369 mmol, 1 eq) in THF (3.0 mL) was added and stirred at reflux for 2 hours. The reaction mixture was allowed to cool to room temperature before concentrated *in vacuo* and purified by flash chromatography (10:1 Pet/EtOAc) to afford the title compound as a colourless oil (80 mg, 70%).  $[\alpha]_D^{20} +2.3$  (*c* 3.45, CHCl<sub>3</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2975, 2930, 2872, 1698; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_H$  0.96 (9H, s), 1.48 (9H, s), 1.80 (3H, s), 2.35 (1H, d, *J* = 13.6 Hz), 3.04 (1H, bs), 4.03 (1H, d, *J* = 8.7 Hz), 4.13 (1H, d, *J* = 8.7 Hz), 4.78 (1H, s), 4.93 (1H, s), 5.09 (1H, d, *J* = 17.7 Hz), 5.10 (1H, bs), 5.14 (1H, d, *J* = 11.0 Hz), 6.21 (1H, bs); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_C$  23.8, 27.0, 28.3, 39.1, 43.0, 66.6, 74.8, 80.5, 97.4, 113.7, 115.8, 141.1, 142.0, 153.9; HRMS (ESI, +ve) *m/z* calcd. for C<sub>18</sub>H<sub>31</sub>NO<sub>3</sub>Na 332.2202, found: 332.2193 (M+Na)<sup>+</sup>.

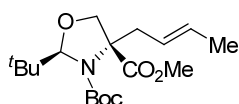
**(4*S*,5*R*)-*tert*-Butyl 4-((*R*)-1-ethoxyallyl)-5-methyl-4-vinyloxazolidine-3-carboxylate (328)**



To a solution of methyltriphenylphosphonium bromide (215 mg, 0.602 mmol, 1.5 eq) in THF (3.0 mL) at 0 °C was added *n*-butyl lithium (1.6M in hexane, 376  $\mu$ L, 0.602 mmol, 1.5 eq) and the reaction turned a dark yellow. After 15 minutes a solution of (4*S*,5*R*)-*tert*-butyl 4-((*R*)-1-ethoxyallyl)-4-(hydroxymethyl)-5-methyloxazolidine-3-carboxylate **326** (120 mg, 0.401 mmol, 1 eq) in THF (3.0 mL) was added and stirred at reflux for 16 hours. The reaction mixture was allowed to cool to room temperature before concentrated *in vacuo* and purified by flash chromatography (10:1 Pet/EtOAc) to afford the title compound as a colourless oil (87 mg, 73%, 5:2 mix of rotamers).  $[\alpha]_D^{20} +67.9$  (*c* 1.40, CHCl<sub>3</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2977, 2936, 2857, 1710, 1692; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_H$  major rotamer 1.10–1.18 (6H, m), 1.45 (9H, s), 3.26–3.38 (1H, m), 3.48–3.61 (1H, m), 4.30–4.42 (1H, m), 4.63–4.67 (1H, m), 4.97 (1H, d, *J* = 3.3 Hz),

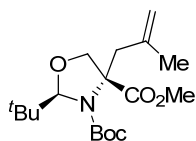
5.13–5.39 (5H, m), 5.60–5.76 (2H, m);  $\delta_{\text{H}}$  minor rotamer 1.10–1.18 (6H, m), 1.43 (9H, s), 3.26–3.38 (1H, m), 3.48–3.61 (1H, m), 4.30–4.42 (1H, m), 4.63–4.67 (1H, m), 4.73 (1H, d,  $J = 3.3$  Hz), 5.13–5.39 (5H, m), 5.60–5.76 (2H, m);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  major rotamer 15.4, 16.7, 28.4, 64.3, 68.9, 77.6, 79.1, 79.3, 79.5, 116.6, 119.4, 132.8, 134.8, 151.4;  $\delta_{\text{C}}$  minor rotamer 15.4, 16.8, 28.4, 64.7, 68.6, 78.7, 79.6, 80.0, 80.8, 116.3, 119.5, 133.5, 135.0, 152.2; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{16}\text{H}_{27}\text{NO}_4\text{Na}$  320.1838, found: 320.1856 ( $\text{M}+\text{Na}$ ) $^{+}$ .

**(2*R*,4*S*)-3-*tert*-Butyl 4-methyl 4-((*E*)-but-2-enyl)-2-*tert*-butyloxazolidine-3,4-dicarboxylate (333a)**



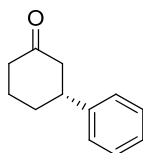
To a solution of (2*R*,4*S*)-3-*tert*-butyl 4-methyl 2-*tert*-butyloxazolidine-3,4-dicarboxylate **249** (1.44 g, 5 mmol, 1 eq) and crotyl bromide (5.14 mL, 50 mmol, 10 eq) in THF (15 mL) at -84 °C was added LHMDS (1M in THF, 15 mL, 15 mmol, 3 eq) *via* syringe pump at a rate of 10 mL/hr and allowed to stir at -84 °C for 16 hours. Quenched with  $\text{NH}_4\text{Cl}$  (sat.) (30 mL), diluted with water (30 mL) and extracted with EtOAc (1  $\times$  50 mL) and DCM (2  $\times$  50 mL). The organics were combined, dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. Purification by flash chromatography affords the title compound as a colourless oil (1.54 g, 90%, 6:1 mix of rotamers).  $[\alpha]_{\text{D}}^{20} +26.7$  ( $c$  1.35,  $\text{CHCl}_3$ ); FTIR (film/ $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 2961, 2911, 2881, 1743, 1708;  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  major rotamer 0.98 (9H, s), 1.44 (9H, s), 1.67 (3H, dd,  $J = 6.3, 1.0$  Hz), 2.62 (1H, app. d,  $J = 15.1$  Hz), 3.01 (1H, bs), 3.75 (3H, s), 4.05 (1H, d,  $J = 8.5$  Hz), 4.22 (1H, dd,  $J = 8.5, 1.5$  Hz), 5.04 (1H, s), 5.36–5.47 (1H, m), 5.51–5.59 (1H, m);  $\delta_{\text{H}}$  minor rotamer 0.99 (9H, s), 1.43 (9H, s), 1.64 (3H, dd,  $J = 6.3, 1.0$  Hz), 2.74 (1H, app. d,  $J = 15.1$  Hz), 3.01 (1H, bs), 3.76 (3H, s), 3.99 (1H, d,  $J = 8.5$  Hz), 4.24 (1H, dd,  $J = 8.5, 1.5$  Hz), 5.11 (1H, s), 5.36–5.47 (1H, m), 5.60–5.69 (1H, m);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  major rotamer 18.1, 26.5, 28.2, 37.9, 39.4, 52.3, 68.8, 75.3, 80.7, 98.0, 124.2, 130.2, 153.2, 172.4;  $\delta_{\text{C}}$  minor rotamer 13.1, 26.5, 28.2, 37.9, 39.4, 52.3, 68.8, 75.3, 80.8, 98.0, 123.4, 127.9, 153.2, 172.5; HRMS (ESI, +ve)  $m/z$  calcd. for  $\text{C}_{18}\text{H}_{31}\text{NO}_5\text{Na}$  364.2100, found: 364.2116 ( $\text{M}+\text{Na}$ ) $^{+}$ .

**(2*R*,4*S*)-3-*tert*-Butyl 4-methyl 2-*tert*-butyl-4-(2-methylallyl)oxazolidine-3,4-dicarboxylate (333b)**



To a solution of (2*R*,4*S*)-3-*tert*-butyl 4-methyl 2-*tert*-butyloxazolidine-3,4-dicarboxylate **249** (1.44 g, 5 mmol, 1 eq) and crotyl bromide (5.14 mL, 50 mmol, 10 eq) in THF (15 mL) at -84 °C was added LHMDS (1M in THF, 15 mL, 15 mmol, 3 eq) *via* syringe pump at a rate of 10 mL/hr and allowed to stir at -84 °C for 16 hours. Quenched with NH<sub>4</sub>Cl (sat.) (30 mL), diluted with water (30 mL) and extracted with EtOAc (1 × 50 mL) and DCM (2 × 50 mL). The organics were combined, dried over MgSO<sub>4</sub> and concentrated *in vacuo*. Purification by flash chromatography affords the title compound as a colourless oil (1.54 g, 90%).  $[\alpha]_D^{20} +11.5$  (*c* 1.92, CHCl<sub>3</sub>); FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2975, 2957, 2908, 2878, 1743, 1708; <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_H$  0.99 (9H, s), 1.45 (9H, s), 1.79 (3H, s), 2.66 (1H, d, *J* = 14.2 Hz), 3.12 (1H, bs), 3.75 (3H, s), 4.14 (1H, d, *J* = 8.2 Hz), 4.20 (1H, d, *J* = 8.2 Hz), 4.79 (1H, s), 4.93 (1H, s), 5.06 (1H, s); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_C$  23.6, 26.7, 28.2, 39.5, 40.9, 52.4, 68.9, 74.0, 80.9, 97.8, 116.4, 140.8, 152.9, 172.4; HRMS (ESI, +ve) *m/z* calcd. for C<sub>18</sub>H<sub>31</sub>NO<sub>5</sub>Na 364.2100, found: 364.2102 (M+Na)<sup>+</sup>.

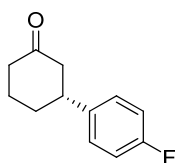
**(*R*)-3-Phenylcyclohexanone (*ent*-304)**



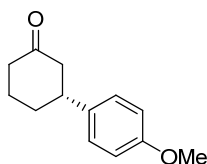
Phenylboronic acid (60 mg, 0.50 mmol), bis(ethylene)rhodium(I) chloride dimer (3.2 mg, 8.25 μmol), (2*R*,4*R*)-*tert*-butyl 4-allyl-2-*tert*-butyl-4-vinyloxazolidine-3-carboxylate **327c** (5.8 mg, 19.8 μmol), 2-cyclohexenone (32 μL, 0.330 mmol) and KOH (0.075M in water, 0.45 mL, 33 μmol) were combined according to General Procedure X. Purification by flash chromatography (10:1 Pet/EtOAc) affords the methyl ester as a

colourless oil (58 mg, 100%, 88% ee). Chiral HPLC analysis performed using Chiralpak AD column (hexane/2-propanol, 99:1, 0.5 mL/min, 214 nm);  $t_R$ : 23.3 min (minor), 27.8 min (major).  $[\alpha]_D^{20} +16.0$  ( $c$  1.88,  $\text{CHCl}_3$ ), lit.<sup>268</sup>  $[\alpha]_D^{20} +17.2$  ( $c$  1.0,  $\text{CHCl}_3$ , 94% ee);  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_H$  1.74–1.93 (2H, m), 2.07–2.14 (1H, m), 2.17 (1H, ddd,  $J = 13.0, 6.3, 3.2$  Hz), 2.35–2.65 (4H, m), 3.03 (1H, tt,  $J = 11.8, 3.9$  Hz), 7.22–7.28 (3H, m), 7.35 (2H, app. t,  $J = 7.5$  Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_C$  25.6, 32.8, 41.2, 44.8, 49.0, 126.6, 126.7, 128.7, 144.4, 211.0. All analytical data in accordance with reported literature values.<sup>268</sup>

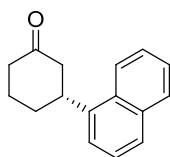
**(*R*)-3-(4-Fluorophenyl)cyclohexanone (334a)**



4-Fluorophenyl boronic acid (70 mg, 0.50 mmol), bis(ethylene)rhodium(I) chloride dimer (3.2 mg, 8.25  $\mu\text{mol}$ ), (*2R,4R*)-*tert*-butyl 4-allyl-2-*tert*-butyl-4-vinyloxazolidine-3-carboxylate **327c** (5.8 mg, 19.8  $\mu\text{mol}$ ), 2-cyclohexenone (32  $\mu\text{L}$ , 0.330 mmol) and KOH (0.075M in water, 0.45 mL, 33  $\mu\text{mol}$ ) were combined according to General Procedure X. Purification by flash chromatography (10:1 Pet/EtOAc) affords the methyl ester as a colourless oil (60 mg, 95%, 91% ee). Chiral HPLC analysis performed using Chiralpak AD column (hexane/2-propanol, 97:3, 1 mL/min, 214 nm);  $t_R$ : 9.6 min (minor), 12.0 min (major).  $[\alpha]_D^{20} +12.4$  ( $c$  2.5,  $\text{CHCl}_3$ ), lit.<sup>268</sup>  $[\alpha]_D^{20} +16.0$  ( $c$  1.05,  $\text{CHCl}_3$ , 93% ee);  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_H$  1.71–1.90 (2H, m), 2.01–2.11 (1H, m), 2.11–2.21 (1H, m), 2.32–2.43 (1H, m), 2.43–2.54 (2H, m), 2.54–2.63 (1H, m), 2.94–3.08 (1H, m), 6.97–7.06 (2H, m), 7.14–7.23 (2H, m);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_C$  25.4, 32.9, 41.1, 44.0, 49.1, 115.4 (d,  $J = 21.4$  Hz), 128.0 (d,  $J = 8.0$  Hz), 140.1 (d,  $J = 3.0$  Hz), 161.5 (d,  $J = 243.7$  Hz), 210.6. All analytical data in accordance with reported literature values.<sup>268</sup>

**(*R*)-3-(4-Methoxyphenyl)cyclohexanone (334b)**

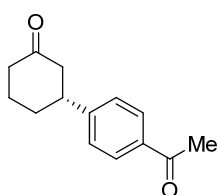
4-Methoxyphenyl boronic acid (76 mg, 0.50 mmol), bis(ethylene)rhodium(I) chloride dimer (3.2 mg, 8.25  $\mu$ mol), (*2R,4R*)-*tert*-butyl 4-allyl-2-*tert*-butyl-4-vinyloxazolidine-3-carboxylate **327c** (5.8 mg, 19.8  $\mu$ mol), 2-cyclohexenone (32  $\mu$ L, 0.330 mmol) and KOH (0.075M in water, 0.45 mL, 33  $\mu$ mol) were combined according to General Procedure X. Purification by flash chromatography (10:1 Pet/EtOAc) affords the methyl ester as a colourless oil (62 mg, 93%, 84% ee). Chiral HPLC analysis performed using Chiralcel OJ column (hexane/2-propanol, 97:3, 0.8 mL/min, 214 nm);  $t_R$ : 26.4 min (major), 31.5 min (minor).  $[\alpha]_D^{20} +13.8$  ( $c$  2.4,  $\text{CHCl}_3$ ), lit.<sup>268</sup>  $[\alpha]_D^{20} +14.0$  ( $c$  0.95,  $\text{CHCl}_3$ , 93% ee);  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_H$  1.73–1.89 (2H, m), 2.04–2.11 (1H, m), 2.12–2.20 (1H, m), 2.33–2.64 (4H, m), 2.99 (1H, tt,  $J = 11.8, 3.9$  Hz), 3.81 (3H, s), 6.89 (2H, app. d,  $J = 8.6$  Hz), 7.16 (2H, app. d,  $J = 8.6$  Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_C$  25.5, 33.0, 41.2, 44.0, 49.2, 55.3, 114.0, 127.5, 136.6, 158.3, 211.2. All analytical data in accordance with reported literature values.<sup>268</sup>

**(*R*)-3-(Naphthalen-1-yl)cyclohexanone (334c)**

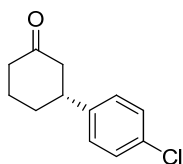
1-Naphthaleneboronic acid (86 mg, 0.50 mmol), bis(ethylene)rhodium(I) chloride dimer (3.2 mg, 8.25  $\mu$ mol), (*2R,4R*)-*tert*-butyl 4-allyl-2-*tert*-butyl-4-vinyloxazolidine-3-carboxylate **327c** (5.8 mg, 19.8  $\mu$ mol), 2-cyclohexenone (32  $\mu$ L, 0.330 mmol) and KOH (0.075M in water, 0.45 mL, 33  $\mu$ mol) were combined according to General Procedure X. Purification by flash chromatography (10:1 Pet/EtOAc) affords the methyl ester as a colourless oil (74 mg, 100%, 73% ee). Chiral HPLC analysis performed using Chiralcel OD-H column (hexane/2-propanol, 90:10, 0.8 mL/min, 214 nm);  $t_R$ : 17.4 min (major),

24.7 min (minor).  $[\alpha]_{\text{D}}^{20} +31.0$  (*c* 2.97,  $\text{CHCl}_3$ ), lit.<sup>259</sup>  $[\alpha]_{\text{D}}^{20} +48.4$  (*c* 1.05,  $\text{CHCl}_3$ , 82% ee);  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  1.88–2.09 (2H, m), 2.16–2.32 (2H, m), 2.42–2.84 (4H, m), 3.88 (1H, app. t,  $J = 11.3$  Hz), 7.42 (1H, d,  $J = 7.4$  Hz), 7.45–7.59 (3H, m), 7.78 (1H, d,  $J = 8.1$  Hz), 7.90 (1H, d,  $J = 8.1$  Hz), 8.06 (1H, d,  $J = 8.1$  Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  25.6, 32.3, 39.4, 41.5, 48.6, 122.5, 122.7, 125.6, 125.7, 126.2, 127.3, 129.1, 130.9, 134.0, 140.1, 211.2. All analytical data in accordance with reported literature values.<sup>259</sup>

**(*R*)-3-(4-Acetylphenyl)cyclohexanone (334d)**



4-Acetylphenylboronic acid (82 mg, 0.50 mmol), bis(ethylene)rhodium(I) chloride dimer (3.2 mg, 8.25  $\mu\text{mol}$ ), (*2R,4R*)-*tert*-butyl 4-allyl-2-*tert*-butyl-4-vinyloxazolidine-3-carboxylate **327c** (5.8 mg, 19.8  $\mu\text{mol}$ ), 2-cyclohexenone (32  $\mu\text{L}$ , 0.330 mmol) and KOH (0.075M in water, 0.45 mL, 33  $\mu\text{mol}$ ) were combined according to General Procedure X. Purification by flash chromatography (10:1 Pet/EtOAc) affords the methyl ester as a colourless oil (17 mg, 24%, 79% ee). Chiral HPLC analysis performed using Chiralpak AD column (hexane/2-propanol, 90:10, 0.6 mL/min, 214 nm);  $t_{\text{R}}$ : 33.73 min (major), 39.5 min (minor).  $[\alpha]_{\text{D}}^{20} +5.9$  (*c* 0.85,  $\text{CHCl}_3$ ), lit.<sup>257</sup>  $[\alpha]_{\text{D}}^{20} -7.3$  (*c* 1.0,  $\text{CHCl}_3$ , 92% ee for *S*-isomer);  $^1\text{H}$  NMR (500MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  1.74–1.97 (2H, m), 2.04–2.25 (2H, m), 2.35–2.69 (7H, m), 3.03–3.16 (1H, m), 7.33 (2H, app. d,  $J = 8.0$  Hz), 7.94 (2H, app. d,  $J = 8.0$  Hz);  $^{13}\text{C}$  NMR (125MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  25.4, 26.6, 32.4, 41.1, 44.6, 48.4, 126.9, 128.9, 135.8, 149.7, 197.7, 210.3. All analytical data in accordance with reported literature values.<sup>257</sup>

**(*R*)-3-(4-Chlorophenyl)cyclohexanone (334e)**

4-Chlorophenylboronic acid (78 mg, 0.50 mmol), bis(ethylene)rhodium(I) chloride dimer (3.2 mg, 8.25  $\mu$ mol), (*2R,4R*)-*tert*-butyl 4-allyl-2-*tert*-butyl-4-vinyloxazolidine-3-carboxylate **327c** (5.8 mg, 19.8  $\mu$ mol), 2-cyclohexenone (32  $\mu$ L, 0.330 mmol) and KOH (0.075M in water, 0.45 mL, 33  $\mu$ mol) were combined according to General Procedure X. Purification by flash chromatography (10:1 Pet/EtOAc) affords the methyl ester as a colourless oil (60 mg, 87%). Chiral HPLC analysis performed using Chiralpak AD, Chiralcel OD, OD-H or OJ columns unable to afford resolution of enantiomeric peaks.  $[\alpha]_{\text{D}}^{20} +8.2$  (*c* 2.45, CHCl<sub>3</sub>), lit.<sup>301</sup>  $[\alpha]_{\text{D}}^{20} +12.0$  (*c* 0.20, CHCl<sub>3</sub>, 99% ee); <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  1.70–1.90 (2H, m), 2.01–2.23 (2H, m), 2.32–2.63 (4H, m), 2.92–3.07 (1H, m), 7.16 (2H, app. d, *J* = 8.3 Hz), 7.30 (2H, app. d, *J* = 8.3 Hz); <sup>13</sup>C NMR (125MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  25.4, 32.7, 41.1, 44.1, 48.8, 128.0, 128.8, 132.4, 142.8, 210.5. All analytical data in accordance with reported literature values.<sup>301</sup>



## 8. APPENDICES

### 8.1 X-Ray Crystallography Data

#### 8.1.1 X-Ray Data for 252i

**Table 1 - Crystal data and structure refinement for 252i**

Identification code	p10dc3
Empirical formula	C <sub>47</sub> H <sub>66</sub> Cl <sub>2</sub> I <sub>2</sub> N <sub>2</sub> O <sub>12</sub>
Formula weight	1175.72
Temperature	240(2) K
Wavelength	1.54184 Å
Crystal system	Hexagonal
Space group	P6 <sub>1</sub>
Unit cell dimensions	a = 10.9498(2) Å $\alpha$ = 90° b = 10.9498(2) Å $\beta$ = 90° c = 77.5761(19) Å $\gamma$ = 120°
Volume	8055.1(3) Å <sup>3</sup>
Z	6
Density (calculated)	1.454 Mg/m <sup>3</sup>
Absorption coefficient	10.588 mm <sup>-1</sup>
F(000)	3588
Crystal size	0.20 x 0.20 x 0.12 mm
Theta range for data collection	3.42 to 67.47°
Index ranges	-11 ≤ h ≤ 13; -12 ≤ k ≤ 13; -92 ≤ l ≤ 92
Reflections collected	61225
Independent reflections	9351 [R(int) = 0.0644]
Reflections observed (>2σ)	8819
Data Completeness	0.998
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.42759
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	9351 / 30 / 628
Goodness-of-fit on F <sup>2</sup>	1.037
Final R indices [I > 2σ(I)]	R <sub>1</sub> = 0.0498 wR <sub>2</sub> = 0.1255
R indices (all data)	R <sub>1</sub> = 0.0533 wR <sub>2</sub> = 0.1283
Absolute structure parameter	0.015(5)
Largest diff. peak and hole	0.875 and -0.970 eÅ <sup>-3</sup>

Notes:

The asymmetric unit consists of two molecules of the target compound, plus a disordered region of solvent. The latter was modeled as two dichloromethane fragments, present in a 60:40 ratio. C-Cl, Cl...Cl and some ADP restraints were applied in the solvent region, in order to assist convergence.

**Table 2 - Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for 252i.****U(eq) is defined as one third of the trace of the orthogonalized  $U_{ij}$  tensor**

Atom	x	y	z	U(eq)
I(1)	9800(1)	15856(1)	-239(1)	66(1)
I(1A)	6571(1)	3144(1)	9(1)	60(1)
Cl(1)	10641(11)	6294(10)	1115(1)	122(3)
Cl(2)	10214(18)	8438(13)	973(1)	168(4)
Cl(3)	10314(9)	6631(6)	939(1)	142(2)
Cl(4)	12195(6)	9262(6)	824(1)	109(2)
O(1)	9164(5)	11140(5)	-50(1)	50(1)
O(2)	9789(5)	12070(5)	-626(1)	48(1)
O(3)	7799(4)	11731(5)	-495(1)	44(1)
O(4)	11263(6)	10358(6)	-426(1)	58(1)
O(5)	11899(5)	10844(5)	-149(1)	52(1)
O(6)	11289(5)	14281(4)	-360(1)	46(1)
O(7)	6879(4)	2295(5)	377(1)	41(1)
O(2A)	8048(5)	4947(5)	591(1)	54(1)
O(3A)	9262(5)	6221(4)	358(1)	45(1)
O(4A)	9776(5)	3659(5)	806(1)	54(1)
O(5A)	10283(4)	2144(5)	678(1)	46(1)
O(6A)	10757(4)	3609(4)	293(1)	40(1)
N(1)	9316(5)	11358(5)	-344(1)	34(1)
N(1A)	9644(4)	4518(5)	454(1)	32(1)
C(1)	8285(6)	10863(7)	-199(1)	43(1)
C(2)	10525(7)	12294(6)	-89(1)	46(1)
C(3)	10771(5)	11994(6)	-277(1)	34(1)
C(4)	7202(7)	9295(7)	-196(1)	55(2)
C(5)	7930(9)	8399(8)	-211(1)	66(2)
C(6)	6449(10)	9005(11)	-20(1)	87(3)
C(7)	6122(9)	8900(9)	-340(1)	83(3)
C(8)	9045(6)	11761(6)	-501(1)	37(1)
C(9)	7228(7)	12049(7)	-652(1)	52(2)
C(10)	8197(9)	13533(8)	-708(1)	66(2)
C(11)	6975(11)	10973(9)	-790(1)	75(2)
C(12)	5857(9)	11897(13)	-584(1)	84(3)
C(13)	11310(6)	10957(6)	-295(1)	39(1)
C(14)	12591(9)	10019(9)	-159(1)	69(2)
C(15)	11854(6)	13359(5)	-370(1)	39(1)
C(16)	13287(7)	14007(7)	-282(1)	55(2)
C(17)	14353(13)	14123(14)	-358(2)	109(4)
C(18)	11803(6)	15427(6)	-466(1)	41(1)
C(19)	11288(7)	16341(6)	-436(1)	46(1)
C(20)	11710(9)	17522(7)	-538(1)	57(2)
C(21)	12697(9)	17812(7)	-666(1)	61(2)
C(22)	13209(7)	16940(7)	-696(1)	53(2)
C(23)	12789(7)	15744(7)	-596(1)	46(1)
C(1A)	10702(5)	4863(6)	317(1)	37(1)
C(2A)	9487(5)	2454(6)	354(1)	35(1)
C(3A)	9081(5)	3040(5)	509(1)	30(1)
C(4A)	12225(6)	6059(7)	360(1)	51(2)
C(5A)	12757(7)	5712(10)	525(1)	70(2)

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C(6A)	13160(7)	6104(10)	211(1)	72(2)
C(7A)	12318(8)	7488(9)	378(2)	90(3)
C(8A)	8894(6)	5214(6)	478(1)	38(1)
C(9A)	8693(8)	7205(8)	369(1)	58(2)
C(10A)	7125(10)	6408(10)	337(2)	88(3)
C(11A)	9468(13)	8195(10)	218(1)	86(3)
C(12A)	9059(10)	7974(9)	534(1)	69(2)
C(13A)	9761(5)	3000(6)	681(1)	34(1)
C(14A)	10808(8)	1945(9)	841(1)	58(2)
C(15A)	7457(5)	2180(6)	538(1)	34(1)
C(16A)	7017(6)	695(7)	583(1)	47(1)
C(17A)	6314(7)	-399(8)	481(1)	63(2)
C(18A)	5592(5)	2220(6)	375(1)	39(1)
C(19A)	5212(6)	2576(7)	221(1)	43(1)
C(20A)	3931(8)	2549(9)	207(1)	62(2)
C(21A)	3058(8)	2197(12)	344(1)	80(3)
C(22A)	3412(7)	1819(11)	498(1)	75(2)
C(23A)	4681(7)	1833(9)	514(1)	59(2)
C(1S)	9570(30)	6691(13)	1001(5)	145(6)
C(2S)	11081(16)	8366(7)	987(2)	114(4)

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Table 3 - Bond lengths [Å] and angles [°] for 252i

I(1)-C(19)	2.101(6)	I(1A)-C(19A)	2.090(6)
Cl(1)-C(1S)	1.690(2)	Cl(2)-C(1S)	1.690(2)
Cl(3)-C(2S)	1.690(2)	Cl(4)-C(2S)	1.688(2)
O(1)-C(2)	1.424(8)	O(1)-C(1)	1.434(7)
O(2)-C(8)	1.204(7)	O(3)-C(8)	1.348(7)
O(3)-C(9)	1.485(7)	O(4)-C(13)	1.194(8)
O(5)-C(13)	1.340(7)	O(5)-C(14)	1.442(8)
O(6)-C(18)	1.363(7)	O(6)-C(15)	1.427(7)
O(7)-C(18A)	1.369(6)	O(7)-C(15A)	1.431(6)
O(2A)-C(8A)	1.203(7)	O(3A)-C(8A)	1.337(7)
O(3A)-C(9A)	1.492(7)	O(4A)-C(13A)	1.203(7)
O(5A)-C(13A)	1.320(7)	O(5A)-C(14A)	1.448(7)
O(6A)-C(2A)	1.413(6)	O(6A)-C(1A)	1.416(7)
N(1)-C(8)	1.379(7)	N(1)-C(3)	1.476(7)
N(1)-C(1)	1.492(7)	N(1A)-C(8A)	1.383(7)
N(1A)-C(1A)	1.475(7)	N(1A)-C(3A)	1.477(7)
C(1)-C(4)	1.522(9)	C(1)-H(1)	0.9900
C(2)-C(3)	1.548(7)	C(2)-H(2A)	0.9800
C(2)-H(2B)	0.9800	C(3)-C(13)	1.525(7)
C(3)-C(15)	1.545(7)	C(4)-C(7)	1.522(11)
C(4)-C(6)	1.546(10)	C(4)-C(5)	1.548(11)
C(5)-H(5A)	0.9700	C(5)-H(5B)	0.9700
C(5)-H(5C)	0.9700	C(6)-H(6A)	0.9700
C(6)-H(6B)	0.9700	C(6)-H(6C)	0.9700
C(7)-H(7A)	0.9700	C(7)-H(7B)	0.9700
C(7)-H(7C)	0.9700	C(9)-C(10)	1.494(11)
C(9)-C(11)	1.513(11)	C(9)-C(12)	1.520(11)
C(10)-H(10A)	0.9700	C(10)-H(10B)	0.9700
C(10)-H(10C)	0.9700	C(11)-H(11A)	0.9700
C(11)-H(11B)	0.9700	C(11)-H(11C)	0.9700
C(12)-H(12A)	0.9700	C(12)-H(12B)	0.9700
C(12)-H(12C)	0.9700	C(14)-H(14A)	0.9700
C(14)-H(14B)	0.9700	C(14)-H(14C)	0.9700
C(15)-C(16)	1.521(9)	C(15)-H(15)	0.9900
C(16)-C(17)	1.254(15)	C(16)-H(16)	0.9400
C(17)-H(17A)	0.9400	C(17)-H(17B)	0.9400
C(18)-C(23)	1.391(8)	C(18)-C(19)	1.391(8)
C(19)-C(20)	1.381(9)	C(20)-C(21)	1.386(11)
C(20)-H(20)	0.9400	C(21)-C(22)	1.348(11)
C(21)-H(21)	0.9400	C(22)-C(23)	1.389(10)
C(22)-H(22)	0.9400	C(23)-H(23)	0.9400
C(1A)-C(4A)	1.555(8)	C(1A)-H(1A)	0.9900
C(2A)-C(3A)	1.533(7)	C(2A)-H(2A1)	0.9800
C(2A)-H(2A2)	0.9800	C(3A)-C(13A)	1.536(7)
C(3A)-C(15A)	1.556(6)	C(4A)-C(7A)	1.523(11)
C(4A)-C(6A)	1.527(10)	C(4A)-C(5A)	1.532(11)
C(5A)-H(5A1)	0.9700	C(5A)-H(5A2)	0.9700
C(5A)-H(5A3)	0.9700	C(6A)-H(6A1)	0.9700
C(6A)-H(6A2)	0.9700	C(6A)-H(6A3)	0.9700
C(7A)-H(7A1)	0.9700	C(7A)-H(7A2)	0.9700
C(7A)-H(7A3)	0.9700	C(9A)-C(12A)	1.476(11)

C(9A)-C(10A)	1.508(11)	C(9A)-C(11A)	1.531(13)
C(10A)-H(10D)	0.9700	C(10A)-H(10E)	0.9700
C(10A)-H(10F)	0.9700	C(11A)-H(11D)	0.9700
C(11A)-H(11E)	0.9700	C(11A)-H(11F)	0.9700
C(12A)-H(12D)	0.9700	C(12A)-H(12E)	0.9700
C(12A)-H(12F)	0.9700	C(14A)-H(14D)	0.9700
C(14A)-H(14E)	0.9700	C(14A)-H(14F)	0.9700
C(15A)-C(16A)	1.490(8)	C(15A)-H(15A)	0.9900
C(16A)-C(17A)	1.316(10)	C(16A)-H(16A)	0.9400
C(17A)-H(17C)	0.9400	C(17A)-H(17D)	0.9400
C(18A)-C(23A)	1.383(8)	C(18A)-C(19A)	1.389(9)
C(19A)-C(20A)	1.391(8)	C(20A)-C(21A)	1.355(12)
C(20A)-H(20A)	0.9400	C(21A)-C(22A)	1.382(14)
C(21A)-H(21A)	0.9400	C(22A)-C(23A)	1.388(10)
C(22A)-H(22A)	0.9400	C(23A)-H(23A)	0.9400
C(1S)-H(1S1)	0.9800	C(1S)-H(1S2)	0.9800
C(2S)-H(2S1)	0.9800	C(2S)-H(2S2)	0.9800
C(2)-O(1)-C(1)	108.0(4)	C(8)-O(3)-C(9)	120.5(5)
C(13)-O(5)-C(14)	116.3(5)	C(18)-O(6)-C(15)	119.6(4)
C(18A)-O(7)-C(15A)	119.3(4)	C(8A)-O(3A)-C(9A)	119.8(5)
C(13A)-O(5A)-C(14A)	116.1(5)	C(2A)-O(6A)-C(1A)	108.9(4)
C(8)-N(1)-C(3)	120.8(4)	C(8)-N(1)-C(1)	122.6(4)
C(3)-N(1)-C(1)	110.5(4)	C(8A)-N(1A)-C(1A)	124.0(4)
C(8A)-N(1A)-C(3A)	121.9(4)	C(1A)-N(1A)-C(3A)	109.4(4)
O(1)-C(1)-N(1)	103.0(4)	O(1)-C(1)-C(4)	106.8(5)
N(1)-C(1)-C(4)	116.2(5)	O(1)-C(1)-H(1)	110.2
N(1)-C(1)-H(1)	110.2	C(4)-C(1)-H(1)	110.2
O(1)-C(2)-C(3)	103.3(4)	O(1)-C(2)-H(2A)	111.1
C(3)-C(2)-H(2A)	111.1	O(1)-C(2)-H(2B)	111.1
C(3)-C(2)-H(2B)	111.1	H(2A)-C(2)-H(2B)	109.1
N(1)-C(3)-C(13)	110.2(4)	N(1)-C(3)-C(15)	114.7(4)
C(13)-C(3)-C(15)	106.3(4)	N(1)-C(3)-C(2)	99.7(4)
C(13)-C(3)-C(2)	114.7(5)	C(15)-C(3)-C(2)	111.4(4)
C(1)-C(4)-C(7)	111.5(6)	C(1)-C(4)-C(6)	106.2(6)
C(7)-C(4)-C(6)	109.3(7)	C(1)-C(4)-C(5)	110.9(6)
C(7)-C(4)-C(5)	109.7(7)	C(6)-C(4)-C(5)	109.1(7)
C(4)-C(5)-H(5A)	109.5	C(4)-C(5)-H(5B)	109.5
H(5A)-C(5)-H(5B)	109.5	C(4)-C(5)-H(5C)	109.5
H(5A)-C(5)-H(5C)	109.5	H(5B)-C(5)-H(5C)	109.5
C(4)-C(6)-H(6A)	109.5	C(4)-C(6)-H(6B)	109.5
H(6A)-C(6)-H(6B)	109.5	C(4)-C(6)-H(6C)	109.5
H(6A)-C(6)-H(6C)	109.5	H(6B)-C(6)-H(6C)	109.5
C(4)-C(7)-H(7A)	109.5	C(4)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7B)	109.5	C(4)-C(7)-H(7C)	109.5
H(7A)-C(7)-H(7C)	109.5	H(7B)-C(7)-H(7C)	109.5
O(2)-C(8)-O(3)	124.5(5)	O(2)-C(8)-N(1)	125.6(5)
O(3)-C(8)-N(1)	109.9(4)	O(3)-C(9)-C(10)	109.9(6)
O(3)-C(9)-C(11)	109.4(5)	C(10)-C(9)-C(11)	113.2(7)
O(3)-C(9)-C(12)	101.5(6)	C(10)-C(9)-C(12)	110.2(7)
C(11)-C(9)-C(12)	111.9(7)	C(9)-C(10)-H(10A)	109.5
C(9)-C(10)-H(10B)	109.5	H(10A)-C(10)-H(10B)	109.5
C(9)-C(10)-H(10C)	109.5	H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5	C(9)-C(11)-H(11A)	109.5
C(9)-C(11)-H(11B)	109.5	H(11A)-C(11)-H(11B)	109.5

C(9)-C(11)-H(11C)	109.5	H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5	C(9)-C(12)-H(12A)	109.5
C(9)-C(12)-H(12B)	109.5	H(12A)-C(12)-H(12B)	109.5
C(9)-C(12)-H(12C)	109.5	H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5	O(4)-C(13)-O(5)	123.9(5)
O(4)-C(13)-C(3)	124.1(5)	O(5)-C(13)-C(3)	112.0(5)
O(5)-C(14)-H(14A)	109.5	O(5)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5	O(5)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5	H(14B)-C(14)-H(14C)	109.5
O(6)-C(15)-C(16)	110.9(5)	O(6)-C(15)-C(3)	105.3(4)
C(16)-C(15)-C(3)	110.9(5)	O(6)-C(15)-H(15)	109.9
C(16)-C(15)-H(15)	109.9	C(3)-C(15)-H(15)	109.9
C(17)-C(16)-C(15)	122.0(9)	C(17)-C(16)-H(16)	119.0
C(15)-C(16)-H(16)	119.0	C(16)-C(17)-H(17A)	120.0
C(16)-C(17)-H(17B)	120.0	H(17A)-C(17)-H(17B)	120.0
O(6)-C(18)-C(23)	125.4(5)	O(6)-C(18)-C(19)	115.8(5)
C(23)-C(18)-C(19)	118.8(5)	C(20)-C(19)-C(18)	120.9(6)
C(20)-C(19)-I(1)	120.4(5)	C(18)-C(19)-I(1)	118.6(4)
C(19)-C(20)-C(21)	118.9(6)	C(19)-C(20)-H(20)	120.6
C(21)-C(20)-H(20)	120.6	C(22)-C(21)-C(20)	120.9(6)
C(22)-C(21)-H(21)	119.5	C(20)-C(21)-H(21)	119.5
C(21)-C(22)-C(23)	120.8(7)	C(21)-C(22)-H(22)	119.6
C(23)-C(22)-H(22)	119.6	C(22)-C(23)-C(18)	119.6(6)
C(22)-C(23)-H(23)	120.2	C(18)-C(23)-H(23)	120.2
O(6A)-C(1A)-N(1A)	104.8(4)	O(6A)-C(1A)-C(4A)	107.3(4)
N(1A)-C(1A)-C(4A)	116.0(5)	O(6A)-C(1A)-H(1A)	109.5
N(1A)-C(1A)-H(1A)	109.5	C(4A)-C(1A)-H(1A)	109.5
O(6A)-C(2A)-C(3A)	104.4(4)	O(6A)-C(2A)-H(2A1)	110.9
C(3A)-C(2A)-H(2A1)	110.9	O(6A)-C(2A)-H(2A2)	110.9
C(3A)-C(2A)-H(2A2)	110.9	H(2A1)-C(2A)-H(2A2)	108.9
N(1A)-C(3A)-C(2A)	100.5(4)	N(1A)-C(3A)-C(13A)	109.8(4)
C(2A)-C(3A)-C(13A)	115.0(4)	N(1A)-C(3A)-C(15A)	115.4(4)
C(2A)-C(3A)-C(15A)	109.9(4)	C(13A)-C(3A)-C(15A)	106.5(4)
C(7A)-C(4A)-C(6A)	109.9(7)	C(7A)-C(4A)-C(5A)	109.7(8)
C(6A)-C(4A)-C(5A)	107.9(6)	C(7A)-C(4A)-C(1A)	112.2(5)
C(6A)-C(4A)-C(1A)	106.7(6)	C(5A)-C(4A)-C(1A)	110.3(5)
C(4A)-C(5A)-H(5A1)	109.5	C(4A)-C(5A)-H(5A2)	109.5
H(5A1)-C(5A)-H(5A2)	109.5	C(4A)-C(5A)-H(5A3)	109.5
H(5A1)-C(5A)-H(5A3)	109.5	H(5A2)-C(5A)-H(5A3)	109.5
C(4A)-C(6A)-H(6A1)	109.5	C(4A)-C(6A)-H(6A2)	109.5
H(6A1)-C(6A)-H(6A2)	109.5	C(4A)-C(6A)-H(6A3)	109.5
H(6A1)-C(6A)-H(6A3)	109.5	H(6A2)-C(6A)-H(6A3)	109.5
C(4A)-C(7A)-H(7A1)	109.5	C(4A)-C(7A)-H(7A2)	109.5
H(7A1)-C(7A)-H(7A2)	109.5	C(4A)-C(7A)-H(7A3)	109.5
H(7A1)-C(7A)-H(7A3)	109.5	H(7A2)-C(7A)-H(7A3)	109.5
O(2A)-C(8A)-O(3A)	125.7(5)	O(2A)-C(8A)-N(1A)	123.9(5)
O(3A)-C(8A)-N(1A)	110.3(5)	C(12A)-C(9A)-O(3A)	111.4(5)
C(12A)-C(9A)-C(10A)	112.3(8)	O(3A)-C(9A)-C(10A)	109.8(6)
C(12A)-C(9A)-C(11A)	111.4(7)	O(3A)-C(9A)-C(11A)	100.8(6)
C(10A)-C(9A)-C(11A)	110.6(8)	C(9A)-C(10A)-H(10D)	109.5
C(9A)-C(10A)-H(10E)	109.5	H(10D)-C(10A)-H(10E)	109.5
C(9A)-C(10A)-H(10F)	109.5	H(10D)-C(10A)-H(10F)	109.5
H(10E)-C(10A)-H(10F)	109.5	C(9A)-C(11A)-H(11D)	109.5
C(9A)-C(11A)-H(11E)	109.5	H(11D)-C(11A)-H(11E)	109.5
C(9A)-C(11A)-H(11F)	109.5	H(11D)-C(11A)-H(11F)	109.5

H(11E)-C(11A)-H(11F)	109.5	C(9A)-C(12A)-H(12D)	109.5
C(9A)-C(12A)-H(12E)	109.5	H(12D)-C(12A)-H(12E)	109.5
C(9A)-C(12A)-H(12F)	109.5	H(12D)-C(12A)-H(12F)	109.5
H(12E)-C(12A)-H(12F)	109.5	O(4A)-C(13A)-O(5A)	123.8(5)
O(4A)-C(13A)-C(3A)	122.8(5)	O(5A)-C(13A)-C(3A)	113.3(4)
O(5A)-C(14A)-H(14D)	109.5	O(5A)-C(14A)-H(14E)	109.5
H(14D)-C(14A)-H(14E)	109.5	O(5A)-C(14A)-H(14F)	109.5
H(14D)-C(14A)-H(14F)	109.5	H(14E)-C(14A)-H(14F)	109.5
O(7)-C(15A)-C(16A)	112.8(5)	O(7)-C(15A)-C(3A)	104.3(4)
C(16A)-C(15A)-C(3A)	110.0(4)	O(7)-C(15A)-H(15A)	109.9
C(16A)-C(15A)-H(15A)	109.9	C(3A)-C(15A)-H(15A)	109.9
C(17A)-C(16A)-C(15A)	124.9(7)	C(17A)-C(16A)-H(16A)	117.5
C(15A)-C(16A)-H(16A)	117.5	C(16A)-C(17A)-H(17C)	120.0
C(16A)-C(17A)-H(17D)	120.0	H(17C)-C(17A)-H(17D)	120.0
O(7)-C(18A)-C(23A)	125.0(6)	O(7)-C(18A)-C(19A)	115.8(5)
C(23A)-C(18A)-C(19A)	119.2(5)	C(18A)-C(19A)-C(20A)	120.1(6)
C(18A)-C(19A)-I(1A)	119.5(4)	C(20A)-C(19A)-I(1A)	120.3(5)
C(21A)-C(20A)-C(19A)	120.3(7)	C(21A)-C(20A)-H(20A)	119.8
C(19A)-C(20A)-H(20A)	119.8	C(20A)-C(21A)-C(22A)	120.2(6)
C(20A)-C(21A)-H(21A)	119.9	C(22A)-C(21A)-H(21A)	119.9
C(21A)-C(22A)-C(23A)	120.2(7)	C(21A)-C(22A)-H(22A)	119.9
C(23A)-C(22A)-H(22A)	119.9	C(18A)-C(23A)-C(22A)	119.9(7)
C(18A)-C(23A)-H(23A)	120.0	C(22A)-C(23A)-H(23A)	120.0
Cl(2)-C(1S)-Cl(1)	114.1(9)	Cl(2)-C(1S)-H(1S1)	108.7
Cl(1)-C(1S)-H(1S1)	108.7	Cl(2)-C(1S)-H(1S2)	108.7
Cl(1)-C(1S)-H(1S2)	108.7	H(1S1)-C(1S)-H(1S2)	107.6
Cl(4)-C(2S)-Cl(3)	107.4(5)	Cl(4)-C(2S)-H(2S1)	110.2
Cl(3)-C(2S)-H(2S1)	110.2	Cl(4)-C(2S)-H(2S2)	110.2
Cl(3)-C(2S)-H(2S2)	110.2	H(2S1)-C(2S)-H(2S2)	108.5

Symmetry transformations used to generate equivalent atoms:

**Table 4 - Anisotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for 252i. The anisotropic displacement factor exponent takes the form:  $-2 \text{ gpi}^2 [h^2 a^{*2} U11 + \dots + 2 h k a^* b^* U$**

Atom	U11	U22	U33	U23	U13	U12
I(1)	77(1)	56(1)	75(1)	-2(1)	28(1)	41(1)
I(1A)	61(1)	85(1)	43(1)	3(1)	2(1)	42(1)
Cl(1)	155(7)	125(6)	97(5)	-20(4)	3(5)	78(5)
Cl(2)	253(11)	141(7)	101(6)	-11(5)	-29(7)	90(8)
Cl(3)	161(5)	91(3)	141(5)	10(3)	-32(4)	39(3)
Cl(4)	104(3)	127(4)	110(4)	-12(3)	-36(3)	69(3)
O(1)	59(3)	65(3)	25(2)	4(2)	5(2)	30(2)
O(2)	53(2)	67(3)	29(2)	6(2)	8(2)	34(2)
O(3)	42(2)	62(2)	37(2)	6(2)	0(2)	32(2)
O(4)	90(3)	74(3)	41(2)	-9(2)	-4(2)	64(3)
O(5)	67(3)	52(2)	49(3)	-6(2)	-19(2)	39(2)
O(6)	60(2)	36(2)	51(2)	5(2)	17(2)	30(2)
O(7)	25(2)	70(3)	32(2)	2(2)	0(1)	26(2)
O(2A)	60(3)	63(3)	54(3)	5(2)	17(2)	42(2)
O(3A)	57(2)	50(2)	43(2)	6(2)	0(2)	38(2)
O(4A)	69(3)	71(3)	34(2)	-7(2)	-7(2)	43(2)
O(5A)	49(2)	63(3)	41(2)	7(2)	1(2)	39(2)
O(6A)	28(2)	48(2)	44(2)	1(2)	9(2)	20(2)
N(1)	36(2)	41(2)	27(2)	1(2)	1(2)	21(2)
N(1A)	25(2)	39(2)	36(2)	1(2)	3(2)	18(2)
C(1)	48(3)	59(3)	31(3)	3(2)	7(2)	34(3)
C(2)	60(4)	47(3)	32(3)	-8(2)	1(2)	28(3)
C(3)	38(3)	41(3)	27(3)	-5(2)	-1(2)	22(2)
C(4)	49(3)	56(4)	51(4)	18(3)	11(3)	21(3)
C(5)	78(5)	51(4)	65(5)	11(3)	-3(4)	28(4)
C(6)	79(6)	91(6)	80(7)	38(5)	39(5)	35(5)
C(7)	60(5)	64(5)	87(7)	21(4)	-12(4)	1(4)
C(8)	43(3)	45(3)	31(3)	-1(2)	0(2)	29(2)
C(9)	54(4)	61(4)	47(4)	4(3)	-12(3)	35(3)
C(10)	76(5)	66(4)	64(5)	5(3)	-13(4)	42(4)
C(11)	100(6)	64(4)	51(4)	0(3)	-27(4)	34(4)
C(12)	64(5)	129(8)	86(6)	12(6)	-9(4)	69(6)
C(13)	40(3)	40(3)	38(3)	3(2)	-2(2)	21(2)
C(14)	80(5)	68(4)	85(6)	-12(4)	-31(4)	57(4)
C(15)	48(3)	33(3)	40(3)	-1(2)	4(2)	23(2)
C(16)	46(3)	52(3)	54(4)	-3(3)	-5(3)	14(3)
C(17)	84(7)	107(9)	140(12)	-2(8)	-8(7)	51(6)
C(18)	49(3)	32(3)	41(3)	-1(2)	5(2)	20(2)
C(19)	55(3)	36(3)	44(3)	-5(2)	1(3)	21(3)
C(20)	84(5)	39(3)	55(4)	-3(3)	2(3)	36(3)
C(21)	82(5)	47(3)	50(4)	7(3)	5(3)	30(3)
C(22)	59(4)	49(3)	39(4)	0(3)	7(3)	18(3)
C(23)	52(3)	43(3)	42(3)	-5(2)	5(3)	23(3)
C(1A)	30(2)	43(3)	38(3)	6(2)	6(2)	19(2)
C(2A)	23(2)	40(3)	35(3)	-5(2)	2(2)	11(2)
C(3A)	23(2)	39(3)	31(3)	2(2)	3(2)	17(2)
C(4A)	27(3)	51(3)	66(4)	7(3)	5(3)	13(2)
C(5A)	40(3)	81(5)	66(5)	-3(4)	-15(3)	13(3)



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C(6A)	37(3)	84(5)	75(6)	25(4)	22(3)	15(3)
C(7A)	41(4)	50(4)	158(10)	3(5)	6(5)	8(3)
C(8A)	36(3)	42(3)	39(3)	1(2)	1(2)	23(2)
C(9A)	77(5)	58(4)	64(4)	-5(3)	-14(3)	52(4)
C(10A)	74(5)	80(6)	138(9)	-29(6)	-43(5)	60(5)
C(11A)	135(9)	81(6)	79(6)	20(5)	1(6)	81(6)
C(12A)	83(5)	62(4)	82(6)	-9(4)	-13(4)	52(4)
C(13A)	26(2)	42(3)	32(3)	2(2)	4(2)	15(2)
C(14A)	55(4)	94(5)	41(3)	15(3)	-2(3)	49(4)
C(15A)	23(2)	45(3)	33(3)	2(2)	0(2)	15(2)
C(16A)	33(3)	49(3)	53(4)	7(3)	5(2)	16(2)
C(17A)	44(3)	48(4)	78(5)	-3(3)	-7(3)	10(3)
C(18A)	25(2)	55(3)	41(3)	-1(2)	4(2)	23(2)
C(19A)	32(3)	55(3)	46(3)	-13(3)	-10(2)	26(2)
C(20A)	53(4)	90(5)	65(5)	-16(4)	-20(3)	52(4)
C(21A)	42(4)	122(7)	92(7)	-19(5)	-1(4)	54(5)
C(22A)	37(3)	120(7)	71(6)	-10(5)	7(3)	41(4)
C(23A)	34(3)	97(5)	49(4)	4(3)	13(3)	35(3)
C(1S)	203(10)	132(9)	104(8)	-17(8)	-10(8)	86(9)
C(2S)	117(7)	109(7)	132(7)	-14(6)	-52(6)	68(6)

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**Table 5 - Hydrogen coordinates ( $\times 10^4$ ) and isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for 252i**

Atom	x	y	z	U(eq)
H(1)	7805	11425	-193	51
H(2A)	11242	12315	-12	55
H(2B)	10538	13194	-81	55
H(5A)	8281	8465	-327	99
H(5B)	7255	7423	-184	99
H(5C)	8710	8748	-130	99
H(6A)	7119	9173	72	130
H(6B)	5690	8033	-15	130
H(6C)	6066	9629	-5	130
H(7A)	6586	9045	-450	125
H(7B)	5690	9485	-332	125
H(7C)	5401	7916	-328	125
H(10A)	8372	14167	-612	98
H(10B)	7765	13770	-802	98
H(10C)	9081	13626	-747	98
H(11A)	7867	11057	-824	112
H(11B)	6539	11139	-890	112
H(11C)	6355	10032	-746	112
H(12A)	5245	10935	-546	126
H(12B)	5394	12122	-675	126
H(12C)	6057	12537	-488	126
H(14A)	11889	9029	-171	104
H(14B)	13133	10155	-54	104
H(14C)	13218	10318	-258	104
H(15)	11941	13152	-492	47
H(16)	13375	14331	-168	66
H(17A)	14282	13804	-472	131
H(17B)	15224	14528	-300	131
H(20)	11336	18119	-520	68
H(21)	13013	18629	-734	73
H(22)	13859	17142	-786	64
H(23)	13168	15154	-616	55
H(1A)	10375	5095	210	44
H(2A1)	9631	1674	388	41
H(2A2)	8754	2118	265	41
H(5A1)	12690	4799	512	105
H(5A2)	12185	5689	621	105
H(5A3)	13732	6427	544	105
H(6A1)	14129	6824	233	108
H(6A2)	12843	6321	104	108
H(6A3)	13103	5194	200	108
H(7A1)	13102	8087	453	135
H(7A2)	11448	7361	428	135
H(7A3)	12462	7926	266	135
H(10D)	6656	5747	430	132
H(10E)	6931	5898	228	132
H(10F)	6778	7067	331	132
H(11D)	9239	8943	214	129
H(11E)	9178	7668	110	129

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H(11F)	10477	8600	232	129
H(12D)	8584	7315	627	104
H(12E)	8764	8674	532	104
H(12F)	10071	8438	551	104
H(14D)	11085	1236	827	87
H(14E)	10073	1636	928	87
H(14F)	11617	2828	877	87
H(15A)	7185	2615	631	41
H(16A)	7260	526	693	56
H(17C)	6053	-272	370	76
H(17D)	6074	-1307	519	76
H(20A)	3671	2776	101	74
H(21A)	2208	2210	335	96
H(22A)	2791	1552	593	91
H(23A)	4922	1580	619	71
H(1S1)	9391	6237	888	174
H(1S2)	8660	6295	1061	174
H(2S1)	10364	8646	998	137
H(2S2)	11601	8566	1096	137

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Table 6 - Dihedral angles [°] for 252i

Atom1 - Atom2 - Atom3 - Atom4	Dihedral
C(2) - O(1) - C(1) - N(1)	27.7(6)
C(2) - O(1) - C(1) - C(4)	150.7(5)
C(8) - N(1) - C(1) - O(1)	-156.4(5)
C(3) - N(1) - C(1) - O(1)	-3.6(6)
C(8) - N(1) - C(1) - C(4)	87.3(7)
C(3) - N(1) - C(1) - C(4)	-120.0(5)
C(1) - O(1) - C(2) - C(3)	-40.5(6)
C(8) - N(1) - C(3) - C(13)	-104.7(5)
C(1) - N(1) - C(3) - C(13)	102.0(5)
C(8) - N(1) - C(3) - C(15)	15.2(6)
C(1) - N(1) - C(3) - C(15)	-138.1(5)
C(8) - N(1) - C(3) - C(2)	134.3(5)
C(1) - N(1) - C(3) - C(2)	-19.0(5)
O(1) - C(2) - C(3) - N(1)	35.0(5)
O(1) - C(2) - C(3) - C(13)	-82.7(6)
O(1) - C(2) - C(3) - C(15)	156.5(5)
O(1) - C(1) - C(4) - C(7)	174.8(7)
N(1) - C(1) - C(4) - C(7)	-71.0(8)
O(1) - C(1) - C(4) - C(6)	55.8(7)
N(1) - C(1) - C(4) - C(6)	170.0(6)
O(1) - C(1) - C(4) - C(5)	-62.6(7)
N(1) - C(1) - C(4) - C(5)	51.6(8)
C(9) - O(3) - C(8) - O(2)	1.9(9)
C(9) - O(3) - C(8) - N(1)	-176.8(5)
C(3) - N(1) - C(8) - O(2)	35.7(8)
C(1) - N(1) - C(8) - O(2)	-174.3(6)
C(3) - N(1) - C(8) - O(3)	-145.5(5)
C(1) - N(1) - C(8) - O(3)	4.5(7)
C(8) - O(3) - C(9) - C(10)	-63.0(8)
C(8) - O(3) - C(9) - C(11)	61.9(8)
C(8) - O(3) - C(9) - C(12)	-179.6(6)
C(14) - O(5) - C(13) - O(4)	4.4(9)
C(14) - O(5) - C(13) - C(3)	-172.9(6)
N(1) - C(3) - C(13) - O(4)	51.0(8)
C(15) - C(3) - C(13) - O(4)	-73.9(7)
C(2) - C(3) - C(13) - O(4)	162.5(6)
N(1) - C(3) - C(13) - O(5)	-131.7(5)
C(15) - C(3) - C(13) - O(5)	103.4(5)
C(2) - C(3) - C(13) - O(5)	-20.1(7)
C(18) - O(6) - C(15) - C(16)	76.4(7)
C(18) - O(6) - C(15) - C(3)	-163.6(5)
N(1) - C(3) - C(15) - O(6)	54.8(6)
C(13) - C(3) - C(15) - O(6)	176.8(4)
C(2) - C(3) - C(15) - O(6)	-57.5(6)
N(1) - C(3) - C(15) - C(16)	174.7(5)
C(13) - C(3) - C(15) - C(16)	-63.2(6)
C(2) - C(3) - C(15) - C(16)	62.4(6)
O(6) - C(15) - C(16) - C(17)	-127.1(9)
C(3) - C(15) - C(16) - C(17)	116.3(9)

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C(15) - O(6) - C(18) - C(23)	5.2(9)
C(15) - O(6) - C(18) - C(19)	-174.2(5)
O(6) - C(18) - C(19) - C(20)	-178.6(6)
C(23) - C(18) - C(19) - C(20)	1.9(10)
O(6) - C(18) - C(19) - I(1)	-0.5(7)
C(23) - C(18) - C(19) - I(1)	-179.9(5)
C(18) - C(19) - C(20) - C(21)	-2.1(11)
I(1) - C(19) - C(20) - C(21)	179.8(6)
C(19) - C(20) - C(21) - C(22)	2.0(12)
C(20) - C(21) - C(22) - C(23)	-1.7(12)
C(21) - C(22) - C(23) - C(18)	1.5(11)
O(6) - C(18) - C(23) - C(22)	179.0(6)
C(19) - C(18) - C(23) - C(22)	-1.6(9)
C(2A) - O(6A) - C(1A) - N(1A)	22.1(5)
C(2A) - O(6A) - C(1A) - C(4A)	146.0(5)
C(8A) - N(1A) - C(1A) - O(6A)	-156.1(5)
C(3A) - N(1A) - C(1A) - O(6A)	-0.1(5)
C(8A) - N(1A) - C(1A) - C(4A)	85.7(6)
C(3A) - N(1A) - C(1A) - C(4A)	-118.2(5)
C(1A) - O(6A) - C(2A) - C(3A)	-34.7(5)
C(8A) - N(1A) - C(3A) - C(2A)	137.3(5)
C(1A) - N(1A) - C(3A) - C(2A)	-19.4(5)
C(8A) - N(1A) - C(3A) - C(13A)	-101.1(5)
C(1A) - N(1A) - C(3A) - C(13A)	102.2(5)
C(8A) - N(1A) - C(3A) - C(15A)	19.2(7)
C(1A) - N(1A) - C(3A) - C(15A)	-137.4(5)
O(6A) - C(2A) - C(3A) - N(1A)	32.1(5)
O(6A) - C(2A) - C(3A) - C(13A)	-85.8(5)
O(6A) - C(2A) - C(3A) - C(15A)	154.1(4)
O(6A) - C(1A) - C(4A) - C(7A)	176.6(7)
N(1A) - C(1A) - C(4A) - C(7A)	-66.6(8)
O(6A) - C(1A) - C(4A) - C(6A)	56.2(7)
N(1A) - C(1A) - C(4A) - C(6A)	173.0(5)
O(6A) - C(1A) - C(4A) - C(5A)	-60.7(7)
N(1A) - C(1A) - C(4A) - C(5A)	56.1(7)
C(9A) - O(3A) - C(8A) - O(2A)	5.1(9)
C(9A) - O(3A) - C(8A) - N(1A)	-174.0(5)
C(1A) - N(1A) - C(8A) - O(2A)	-178.7(6)
C(3A) - N(1A) - C(8A) - O(2A)	28.1(9)
C(1A) - N(1A) - C(8A) - O(3A)	0.4(7)
C(3A) - N(1A) - C(8A) - O(3A)	-152.8(5)
C(8A) - O(3A) - C(9A) - C(12A)	58.0(9)
C(8A) - O(3A) - C(9A) - C(10A)	-67.0(9)
C(8A) - O(3A) - C(9A) - C(11A)	176.3(6)
C(14A) - O(5A) - C(13A) - O(4A)	4.3(8)
C(14A) - O(5A) - C(13A) - C(3A)	-173.8(5)
N(1A) - C(3A) - C(13A) - O(4A)	52.5(6)
C(2A) - C(3A) - C(13A) - O(4A)	164.9(5)
C(15A) - C(3A) - C(13A) - O(4A)	-73.0(7)
N(1A) - C(3A) - C(13A) - O(5A)	-129.3(4)
C(2A) - C(3A) - C(13A) - O(5A)	-16.9(6)
C(15A) - C(3A) - C(13A) - O(5A)	105.1(5)
C(18A) - O(7) - C(15A) - C(16A)	88.9(6)
C(18A) - O(7) - C(15A) - C(3A)	-151.7(5)
N(1A) - C(3A) - C(15A) - O(7)	55.8(6)

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C(2A) - C(3A) - C(15A) - O(7)	-56.9(5)
C(13A) - C(3A) - C(15A) - O(7)	177.9(4)
N(1A) - C(3A) - C(15A) - C(16A)	177.0(5)
C(2A) - C(3A) - C(15A) - C(16A)	64.3(6)
C(13A) - C(3A) - C(15A) - C(16A)	-60.9(6)
O(7) - C(15A) - C(16A) - C(17A)	7.7(8)
C(3A) - C(15A) - C(16A) - C(17A)	-108.3(7)
C(15A) - O(7) - C(18A) - C(23A)	-10.0(9)
C(15A) - O(7) - C(18A) - C(19A)	169.5(5)
O(7) - C(18A) - C(19A) - C(20A)	-179.2(6)
C(23A) - C(18A) - C(19A) - C(20A)	0.3(10)
O(7) - C(18A) - C(19A) - I(1A)	1.0(7)
C(23A) - C(18A) - C(19A) - I(1A)	-179.4(5)
C(18A) - C(19A) - C(20A) - C(21A)	1.0(11)
I(1A) - C(19A) - C(20A) - C(21A)	-179.2(7)
C(19A) - C(20A) - C(21A) - C(22A)	-2.0(14)
C(20A) - C(21A) - C(22A) - C(23A)	1.7(15)
O(7) - C(18A) - C(23A) - C(22A)	178.9(7)
C(19A) - C(18A) - C(23A) - C(22A)	-0.7(11)
C(21A) - C(22A) - C(23A) - C(18A)	-0.3(14)

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Symmetry transformations used to generate equivalent atoms:

## 8.1.2 X-Ray Data for 266d

Table 1 - Crystal data and structure refinement for 266d

Identification code	k10dc1
Empirical formula	C <sub>18</sub> H <sub>29</sub> N O <sub>5</sub>
Formula weight	339.42
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>
Unit cell dimensions	a = 11.7360(1) Å $\alpha$ = 90° b = 9.9090(1) Å $\beta$ = 90° c = 16.7050(2) Å $\gamma$ = 90°
Volume	1942.66(3) Å <sup>3</sup>
Z	4
Density (calculated)	1.161 Mg/m <sup>3</sup>
Absorption coefficient	0.084 mm <sup>-1</sup>
F(000)	736
Crystal size	0.28 x 0.28 x 0.2 mm
Theta range for data collection	3.63 to 27.44°
Index ranges	-15 ≤ h ≤ 15; -12 ≤ k ≤ 12; -21 ≤ l ≤ 21
Reflections collected	37055
Independent reflections	4426 [R(int) = 0.0368]
Reflections observed (>2σ)	4098
Data Completeness	0.995
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.984 and 0.908
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	4426 / 2 / 234
Goodness-of-fit on F <sup>2</sup>	1.007
Final R indices [I > 2σ(I)]	R <sub>1</sub> = 0.0293 wR <sub>2</sub> = 0.0752
R indices (all data)	R <sub>1</sub> = 0.0351 wR <sub>2</sub> = 0.0793
Absolute structure parameter	-0.2(6)
Largest diff. peak and hole	0.196 and -0.189 eÅ <sup>-3</sup>

## Notes:

Allene hydrogens located and refined at 0.98 Å from C13.

**Table 2 - Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for 266d.**  
**U(eq) is defined as one third of the trace of the orthogonalized Uij tensor**

Atom	x	y	z	U(eq)
O(1)	8445(1)	8802(1)	1698(1)	32(1)
O(2)	7094(1)	10157(1)	4017(1)	41(1)
O(3)	7966(1)	11822(1)	3346(1)	31(1)
O(4)	8275(1)	6057(1)	3443(1)	37(1)
O(5)	8703(1)	7821(1)	4256(1)	36(1)
N(1)	8148(1)	8227(1)	3004(1)	26(1)
C(1)	7909(1)	7799(1)	2176(1)	27(1)
C(2)	8501(1)	10031(1)	2137(1)	32(1)
C(3)	8564(1)	9625(1)	3037(1)	25(1)
C(4)	6636(1)	7620(1)	1969(1)	32(1)
C(5)	6163(1)	6386(1)	2404(1)	44(1)
C(6)	6565(1)	7372(1)	1064(1)	42(1)
C(7)	5918(1)	8849(1)	2190(1)	42(1)
C(8)	7779(1)	10525(1)	3536(1)	26(1)
C(9)	7346(1)	12803(1)	3813(1)	38(1)
C(10)	9801(1)	9729(1)	3331(1)	28(1)
C(11)	10656(1)	8833(1)	2908(1)	38(1)
C(12)	10090(1)	10553(1)	3903(1)	30(1)
C(13)	10368(1)	11371(1)	4480(1)	38(1)
C(14)	8379(1)	7257(1)	3569(1)	29(1)
C(15)	8881(1)	6992(1)	4980(1)	36(1)
C(16)	7766(1)	6331(2)	5212(1)	47(1)
C(17)	9825(1)	5970(2)	4850(1)	52(1)
C(18)	9225(2)	8056(2)	5585(1)	59(1)



Table 3 - Bond lengths [Å] and angles [°] for 266d

O(1)-C(1)	1.4219(13)	O(1)-C(2)	1.4223(13)
O(2)-C(8)	1.1936(14)	O(3)-C(8)	1.3420(13)
O(3)-C(9)	1.4429(14)	O(4)-C(14)	1.2137(13)
O(5)-C(14)	1.3322(14)	O(5)-C(15)	1.4762(13)
N(1)-C(14)	1.3738(14)	N(1)-C(3)	1.4692(13)
N(1)-C(1)	1.4743(14)	C(1)-C(4)	1.5431(17)
C(1)-H(1)	1.0000	C(2)-C(3)	1.5582(15)
C(2)-H(2A)	0.9900	C(2)-H(2B)	0.9900
C(3)-C(8)	1.5293(15)	C(3)-C(10)	1.5358(16)
C(4)-C(7)	1.5265(17)	C(4)-C(5)	1.5270(17)
C(4)-C(6)	1.5350(16)	C(5)-H(5A)	0.9800
C(5)-H(5B)	0.9800	C(5)-H(5C)	0.9800
C(6)-H(6A)	0.9800	C(6)-H(6B)	0.9800
C(6)-H(6C)	0.9800	C(7)-H(7A)	0.9800
C(7)-H(7B)	0.9800	C(7)-H(7C)	0.9800
C(9)-H(9A)	0.9800	C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800	C(10)-C(12)	1.3024(17)
C(10)-C(11)	1.5144(16)	C(11)-H(11A)	0.9800
C(11)-H(11B)	0.9800	C(11)-H(11C)	0.9800
C(12)-C(13)	1.3013(18)	C(13)-H(13A)	0.979(5)
C(13)-H(13B)	0.981(5)	C(15)-C(18)	1.5155(19)
C(15)-C(16)	1.5143(19)	C(15)-C(17)	1.516(2)
C(16)-H(16A)	0.9800	C(16)-H(16B)	0.9800
C(16)-H(16C)	0.9800	C(17)-H(17A)	0.9800
C(17)-H(17B)	0.9800	C(17)-H(17C)	0.9800
C(18)-H(18A)	0.9800	C(18)-H(18B)	0.9800
C(18)-H(18C)	0.9800		
C(1)-O(1)-C(2)	109.21(8)	C(8)-O(3)-C(9)	115.79(9)
C(14)-O(5)-C(15)	120.82(8)	C(14)-N(1)-C(3)	124.63(9)
C(14)-N(1)-C(1)	118.75(9)	C(3)-N(1)-C(1)	111.66(8)
O(1)-C(1)-N(1)	104.00(8)	O(1)-C(1)-C(4)	112.53(9)
N(1)-C(1)-C(4)	115.29(9)	O(1)-C(1)-H(1)	108.2
N(1)-C(1)-H(1)	108.2	C(4)-C(1)-H(1)	108.2
O(1)-C(2)-C(3)	106.18(8)	O(1)-C(2)-H(2A)	110.5
C(3)-C(2)-H(2A)	110.5	O(1)-C(2)-H(2B)	110.5
C(3)-C(2)-H(2B)	110.5	H(2A)-C(2)-H(2B)	108.7
N(1)-C(3)-C(8)	111.69(9)	N(1)-C(3)-C(10)	112.91(9)
C(8)-C(3)-C(10)	110.85(9)	N(1)-C(3)-C(2)	101.06(8)
C(8)-C(3)-C(2)	110.29(9)	C(10)-C(3)-C(2)	109.63(9)
C(7)-C(4)-C(5)	108.89(11)	C(7)-C(4)-C(6)	109.65(11)
C(5)-C(4)-C(6)	108.66(11)	C(7)-C(4)-C(1)	112.89(10)
C(5)-C(4)-C(1)	109.72(10)	C(6)-C(4)-C(1)	106.94(10)
C(4)-C(5)-H(5A)	109.5	C(4)-C(5)-H(5B)	109.5
H(5A)-C(5)-H(5B)	109.5	C(4)-C(5)-H(5C)	109.5
H(5A)-C(5)-H(5C)	109.5	H(5B)-C(5)-H(5C)	109.5
C(4)-C(6)-H(6A)	109.5	C(4)-C(6)-H(6B)	109.5
H(6A)-C(6)-H(6B)	109.5	C(4)-C(6)-H(6C)	109.5
H(6A)-C(6)-H(6C)	109.5	H(6B)-C(6)-H(6C)	109.5
C(4)-C(7)-H(7A)	109.5	C(4)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7B)	109.5	C(4)-C(7)-H(7C)	109.5

H(7A)-C(7)-H(7C)	109.5	H(7B)-C(7)-H(7C)	109.5
O(2)-C(8)-O(3)	124.18(10)	O(2)-C(8)-C(3)	126.47(10)
O(3)-C(8)-C(3)	109.35(9)	O(3)-C(9)-H(9A)	109.5
O(3)-C(9)-H(9B)	109.5	H(9A)-C(9)-H(9B)	109.5
O(3)-C(9)-H(9C)	109.5	H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5	C(12)-C(10)-C(11)	122.48(11)
C(12)-C(10)-C(3)	121.56(10)	C(11)-C(10)-C(3)	115.95(10)
C(10)-C(11)-H(11A)	109.5	C(10)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5	C(10)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5	H(11B)-C(11)-H(11C)	109.5
C(10)-C(12)-C(13)	179.20(13)	C(12)-C(13)-H(13A)	119.9(10)
C(12)-C(13)-H(13B)	121.3(9)	H(13A)-C(13)-H(13B)	118.7(14)
O(4)-C(14)-O(5)	126.08(10)	O(4)-C(14)-N(1)	123.13(10)
O(5)-C(14)-N(1)	110.79(9)	O(5)-C(15)-C(18)	101.30(9)
O(5)-C(15)-C(16)	109.16(11)	C(18)-C(15)-C(16)	111.07(12)
O(5)-C(15)-C(17)	111.03(11)	C(18)-C(15)-C(17)	111.42(13)
C(16)-C(15)-C(17)	112.32(11)	C(15)-C(16)-H(16A)	109.5
C(15)-C(16)-H(16B)	109.5	H(16A)-C(16)-H(16B)	109.5
C(15)-C(16)-H(16C)	109.5	H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5	C(15)-C(17)-H(17A)	109.5
C(15)-C(17)-H(17B)	109.5	H(17A)-C(17)-H(17B)	109.5
C(15)-C(17)-H(17C)	109.5	H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5	C(15)-C(18)-H(18A)	109.5
C(15)-C(18)-H(18B)	109.5	H(18A)-C(18)-H(18B)	109.5
C(15)-C(18)-H(18C)	109.5	H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5		

Symmetry transformations used to generate equivalent atoms:

**Table 4 - Anisotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for 266d. The anisotropic displacement factor exponent takes the form:  $-2 \pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$**

Atom	U11	U22	U33	U23	U13	U12
O(1)	46(1)	24(1)	25(1)	-2(1)	6(1)	-5(1)
O(2)	48(1)	31(1)	44(1)	-2(1)	21(1)	-7(1)
O(3)	38(1)	18(1)	37(1)	-1(1)	8(1)	1(1)
O(4)	56(1)	19(1)	36(1)	2(1)	-5(1)	-3(1)
O(5)	57(1)	24(1)	26(1)	5(1)	-6(1)	-8(1)
N(1)	37(1)	17(1)	25(1)	0(1)	0(1)	-4(1)
C(1)	36(1)	20(1)	24(1)	0(1)	2(1)	0(1)
C(2)	48(1)	20(1)	27(1)	1(1)	3(1)	-3(1)
C(3)	33(1)	17(1)	26(1)	1(1)	3(1)	-2(1)
C(4)	36(1)	26(1)	33(1)	-3(1)	-2(1)	0(1)
C(5)	39(1)	39(1)	54(1)	6(1)	-5(1)	-9(1)
C(6)	47(1)	43(1)	37(1)	-7(1)	-8(1)	1(1)
C(7)	38(1)	38(1)	49(1)	-7(1)	-4(1)	5(1)
C(8)	30(1)	22(1)	27(1)	0(1)	0(1)	-3(1)
C(9)	45(1)	25(1)	43(1)	-6(1)	7(1)	6(1)
C(10)	31(1)	21(1)	31(1)	2(1)	5(1)	-2(1)
C(11)	36(1)	30(1)	49(1)	-4(1)	11(1)	2(1)
C(12)	27(1)	29(1)	35(1)	2(1)	4(1)	-1(1)
C(13)	37(1)	39(1)	40(1)	-8(1)	1(1)	-5(1)
C(14)	37(1)	22(1)	29(1)	2(1)	1(1)	-3(1)
C(15)	46(1)	34(1)	27(1)	9(1)	-3(1)	-4(1)
C(16)	50(1)	46(1)	45(1)	12(1)	9(1)	-2(1)
C(17)	44(1)	58(1)	54(1)	9(1)	-6(1)	6(1)
C(18)	95(1)	53(1)	31(1)	3(1)	-15(1)	-12(1)

**Table 5 - Hydrogen coordinates ( x 10<sup>4</sup>) and isotropic displacement parameters (Å<sup>2</sup> x 10<sup>3</sup>) for 266d**

Atom	x	y	z	U(eq)
H(1)	8304	6920	2080	32
H(2A)	7816	10588	2034	38
H(2B)	9185	10554	1981	38
H(5A)	6201	6533	2983	66
H(5B)	6616	5590	2262	66
H(5C)	5369	6241	2244	66
H(6A)	7063	6616	919	63
H(6B)	6810	8185	777	63
H(6C)	5778	7156	917	63
H(7A)	5119	8677	2054	63
H(7B)	6190	9638	1893	63
H(7C)	5983	9022	2766	63
H(9A)	6526	12644	3755	56
H(9B)	7531	13713	3624	56
H(9C)	7560	12717	4378	56
H(11A)	11425	9046	3098	57
H(11B)	10612	8989	2329	57
H(11C)	10483	7885	3023	57
H(16A)	7171	7022	5255	71
H(16B)	7855	5875	5729	71
H(16C)	7550	5670	4803	71
H(17A)	9562	5269	4480	78
H(17B)	10029	5556	5364	78
H(17C)	10494	6424	4624	78
H(18A)	9921	8509	5402	89
H(18B)	9366	7627	6104	89
H(18C)	8611	8720	5639	89
H(13A)	10377(15)	11047(16)	5034(4)	50(4)
H(13B)	10605(13)	12303(7)	4372(9)	44(4)

Table 6 - Dihedral angles [°] for 266d

Atom1 - Atom2 - Atom3 - Atom4	Dihedral
C(2) - O(1) - C(1) - N(1)	-26.75(11)
C(2) - O(1) - C(1) - C(4)	98.71(11)
C(14) - N(1) - C(1) - O(1)	-142.06(10)
C(3) - N(1) - C(1) - O(1)	14.18(12)
C(14) - N(1) - C(1) - C(4)	94.26(12)
C(3) - N(1) - C(1) - C(4)	-109.51(11)
C(1) - O(1) - C(2) - C(3)	29.03(12)
C(14) - N(1) - C(3) - C(8)	-85.69(13)
C(1) - N(1) - C(3) - C(8)	119.74(10)
C(14) - N(1) - C(3) - C(10)	40.03(14)
C(1) - N(1) - C(3) - C(10)	-114.54(10)
C(14) - N(1) - C(3) - C(2)	157.05(11)
C(1) - N(1) - C(3) - C(2)	2.47(12)
O(1) - C(2) - C(3) - N(1)	-18.43(12)
O(1) - C(2) - C(3) - C(8)	-136.71(9)
O(1) - C(2) - C(3) - C(10)	100.96(10)
O(1) - C(1) - C(4) - C(7)	-67.46(13)
N(1) - C(1) - C(4) - C(7)	51.60(14)
O(1) - C(1) - C(4) - C(5)	170.90(10)
N(1) - C(1) - C(4) - C(5)	-70.05(12)
O(1) - C(1) - C(4) - C(6)	53.22(12)
N(1) - C(1) - C(4) - C(6)	172.28(10)
C(9) - O(3) - C(8) - O(2)	5.09(17)
C(9) - O(3) - C(8) - C(3)	-175.49(10)
N(1) - C(3) - C(8) - O(2)	19.03(16)
C(10) - C(3) - C(8) - O(2)	-107.82(13)
C(2) - C(3) - C(8) - O(2)	130.57(12)
N(1) - C(3) - C(8) - O(3)	-160.37(9)
C(10) - C(3) - C(8) - O(3)	72.78(11)
C(2) - C(3) - C(8) - O(3)	-48.83(12)
N(1) - C(3) - C(10) - C(12)	-129.69(11)
C(8) - C(3) - C(10) - C(12)	-3.52(14)
C(2) - C(3) - C(10) - C(12)	118.47(11)
N(1) - C(3) - C(10) - C(11)	51.14(13)
C(8) - C(3) - C(10) - C(11)	177.31(9)
C(2) - C(3) - C(10) - C(11)	-60.69(12)
C(11) - C(10) - C(12) - C(13)	-135(11)
C(3) - C(10) - C(12) - C(13)	46(11)
C(15) - O(5) - C(14) - O(4)	-5.36(19)
C(15) - O(5) - C(14) - N(1)	173.52(10)
C(3) - N(1) - C(14) - O(4)	-161.24(11)
C(1) - N(1) - C(14) - O(4)	-8.32(17)
C(3) - N(1) - C(14) - O(5)	19.84(15)
C(1) - N(1) - C(14) - O(5)	172.76(10)
C(14) - O(5) - C(15) - C(18)	-179.70(13)
C(14) - O(5) - C(15) - C(16)	-62.47(15)
C(14) - O(5) - C(15) - C(17)	61.88(15)

## 8.1.3 X-Ray Data for 280

Table 1 - Crystal data and structure refinement for 280

Identification code	k11dc2
Empirical formula	C31 H38 N2 O11
Formula weight	614.63
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2 <sub>1</sub>
Unit cell dimensions	a = 8.9630(1) Å $\alpha = 90^\circ$ b = 10.6200(1) Å $\beta = 103.620(1)^\circ$ c = 16.8130(3) Å $\gamma = 90^\circ$
Volume	1555.38(4) Å <sup>3</sup>
Z	2
Density (calculated)	1.312 Mg/m <sup>3</sup>
Absorption coefficient	0.100 mm <sup>-1</sup>
F(000)	652
Crystal size	0.50 x 0.35 x 0.30 mm
Theta range for data collection	3.80 to 27.47°
Index ranges	-11 ≤ h ≤ 11; -13 ≤ k ≤ 13; -21 ≤ l ≤ 21
Reflections collected	30623
Independent reflections	6989 [R(int) = 0.0300]
Reflections observed (>2σ)	6183
Data Completeness	0.994
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.981 and 0.949
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	6989 / 16 / 436
Goodness-of-fit on F <sup>2</sup>	1.027
Final R indices [I > 2σ(I)]	R1 = 0.0325 wR2 = 0.0761
R indices (all data)	R1 = 0.0404 wR2 = 0.0808
Absolute structure parameter	0.0(5)
Largest diff. peak and hole	0.143 and -0.159 eÅ <sup>-3</sup>

**Table 2 - Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for 280.****U(eq) is defined as one third of the trace of the orthogonalized Uij tensor**

Atom	x	y	z	U(eq)
O(1)	221(1)	816(1)	874(1)	35(1)
O(2)	5153(1)	814(1)	623(1)	31(1)
O(3)	4537(1)	-921(1)	1220(1)	32(1)
O(4)	2293(1)	3138(1)	580(1)	39(1)
O(5)	6594(1)	3044(1)	1361(1)	39(1)
O(6)	7549(1)	4949(1)	1167(1)	43(1)
O(7)	5403(2)	6985(1)	3413(1)	51(1)
O(8)	10033(2)	3088(2)	5424(1)	65(1)
O(9)	11152(2)	4857(1)	5294(1)	66(1)
O(10)	4777(1)	1171(1)	2637(1)	33(1)
O(11)	2717(1)	1042(1)	3204(1)	34(1)
N(1)	2424(1)	683(1)	1863(1)	27(1)
N(2)	10284(2)	3988(2)	5018(1)	49(1)
C(1)	2892(2)	943(1)	1105(1)	26(1)
C(2)	1420(2)	596(1)	464(1)	31(1)
C(3)	750(2)	451(2)	1709(1)	32(1)
C(4)	4259(2)	147(1)	1015(1)	26(1)
C(5)	4519(2)	2067(1)	420(1)	33(1)
C(6)	3437(2)	2288(1)	982(1)	28(1)
C(7)	5802(2)	3000(2)	506(1)	40(1)
C(8)	7402(2)	4090(2)	1611(1)	33(1)
C(9)	8107(2)	4050(2)	2510(1)	32(1)
C(10)	7903(2)	3017(2)	2986(1)	43(1)
C(11)	8617(2)	3002(2)	3815(1)	47(1)
C(12)	9495(2)	4027(2)	4141(1)	39(1)
C(13)	9688(2)	5064(2)	3688(1)	42(1)
C(14)	8988(2)	5064(2)	2861(1)	39(1)
C(15)	230(2)	-903(2)	1858(1)	37(1)
C(16)	-1532(2)	-878(2)	1630(1)	57(1)
C(17)	776(2)	-1899(2)	1336(1)	41(1)
C(18)	798(2)	-1262(2)	2759(1)	54(1)
C(19)	1538(2)	3798(2)	1119(1)	43(1)
C(20)	2608(2)	4635(1)	1717(1)	34(1)
C(21)	3581(2)	5481(2)	1461(1)	41(1)
C(22)	4549(2)	6271(1)	2004(1)	36(1)
C(23)	4527(2)	6233(1)	2826(1)	36(1)
C(24)	3567(2)	5398(2)	3090(1)	49(1)
C(25)	2634(2)	4594(2)	2542(1)	43(1)
C(26)	6425(2)	7840(2)	3156(1)	48(1)
C(27)	3425(2)	982(1)	2591(1)	26(1)
C(28)	3621(2)	1147(2)	4066(1)	36(1)
C(29)	2480(4)	781(3)	4580(2)	43(1)
C(30)	4925(5)	173(4)	4247(4)	39(1)
C(31)	4214(6)	2450(4)	4251(3)	42(1)
C(29A)	2325(9)	1586(12)	4447(4)	91(3)
C(30A)	4347(14)	-33(9)	4297(7)	80(4)
C(31A)	4754(14)	2275(11)	4134(7)	73(3)

Table 3 - Bond lengths [Å] and angles [°] for 280

O(1)-C(3)	1.4256(17)	O(1)-C(2)	1.4261(18)
O(2)-C(4)	1.3518(16)	O(2)-C(5)	1.4563(18)
O(3)-C(4)	1.1950(17)	O(4)-C(6)	1.4127(17)
O(4)-C(19)	1.436(2)	O(5)-C(8)	1.3383(18)
O(5)-C(7)	1.4459(17)	O(6)-C(8)	1.2052(18)
O(7)-C(23)	1.3644(19)	O(7)-C(26)	1.427(2)
O(8)-N(2)	1.225(2)	O(9)-N(2)	1.225(2)
O(10)-C(27)	1.2131(16)	O(11)-C(27)	1.3338(16)
O(11)-C(28)	1.4881(16)	N(1)-C(27)	1.3731(16)
N(1)-C(1)	1.4582(17)	N(1)-C(3)	1.4820(18)
N(2)-C(12)	1.478(2)	C(1)-C(4)	1.5246(19)
C(1)-C(6)	1.5395(19)	C(1)-C(2)	1.5394(17)
C(2)-H(2A)	0.9900	C(2)-H(2B)	0.9900
C(3)-C(15)	1.550(2)	C(3)-H(3)	1.0000
C(5)-C(7)	1.499(2)	C(5)-C(6)	1.522(2)
C(5)-H(5)	1.0000	C(6)-H(6)	1.0000
C(7)-H(7A)	0.9900	C(7)-H(7B)	0.9900
C(8)-C(9)	1.495(2)	C(9)-C(14)	1.383(2)
C(9)-C(10)	1.395(2)	C(10)-C(11)	1.390(2)
C(10)-H(10)	0.9500	C(11)-C(12)	1.380(2)
C(11)-H(11)	0.9500	C(12)-C(13)	1.372(2)
C(13)-C(14)	1.386(2)	C(13)-H(13)	0.9500
C(14)-H(14)	0.9500	C(15)-C(17)	1.526(2)
C(15)-C(18)	1.529(2)	C(15)-C(16)	1.535(2)
C(16)-H(16A)	0.9800	C(16)-H(16B)	0.9800
C(16)-H(16C)	0.9800	C(17)-H(17A)	0.9800
C(17)-H(17B)	0.9800	C(17)-H(17C)	0.9800
C(18)-H(18A)	0.9800	C(18)-H(18B)	0.9800
C(18)-H(18C)	0.9800	C(19)-C(20)	1.505(2)
C(19)-H(19A)	0.9900	C(19)-H(19B)	0.9900
C(20)-C(25)	1.383(2)	C(20)-C(21)	1.389(2)
C(21)-C(22)	1.384(2)	C(21)-H(21)	0.9500
C(22)-C(23)	1.387(2)	C(22)-H(22)	0.9500
C(23)-C(24)	1.380(2)	C(24)-C(25)	1.384(3)
C(24)-H(24)	0.9500	C(25)-H(25)	0.9500
C(26)-H(26A)	0.9800	C(26)-H(26B)	0.9800
C(26)-H(26C)	0.9800	C(28)-C(30A)	1.424(10)
C(28)-C(31)	1.489(5)	C(28)-C(29A)	1.526(7)
C(28)-C(29)	1.536(3)	C(28)-C(30)	1.537(5)
C(28)-C(31A)	1.557(10)	C(29)-H(29A)	0.9800
C(29)-H(29B)	0.9800	C(29)-H(29C)	0.9800
C(30)-H(30A)	0.9800	C(30)-H(30B)	0.9800
C(30)-H(30C)	0.9800	C(31)-H(31A)	0.9800
C(31)-H(31B)	0.9800	C(31)-H(31C)	0.9800
C(29A)-H(29D)	0.9800	C(29A)-H(29E)	0.9800
C(29A)-H(29F)	0.9800	C(30A)-H(30D)	0.9800
C(30A)-H(30E)	0.9800	C(30A)-H(30F)	0.9800
C(31A)-H(31D)	0.9800	C(31A)-H(31E)	0.9800
C(31A)-H(31F)	0.9800		
C(3)-O(1)-C(2)	108.52(10)	C(4)-O(2)-C(5)	110.43(11)



C(6)-O(4)-C(19)	114.02(11)	C(8)-O(5)-C(7)	116.19(11)
C(23)-O(7)-C(26)	117.04(13)	C(27)-O(11)-C(28)	120.48(10)
C(27)-N(1)-C(1)	118.20(11)	C(27)-N(1)-C(3)	128.03(11)
C(1)-N(1)-C(3)	111.52(10)	O(9)-N(2)-O(8)	124.03(16)
O(9)-N(2)-C(12)	117.96(16)	O(8)-N(2)-C(12)	118.01(15)
N(1)-C(1)-C(4)	112.61(10)	N(1)-C(1)-C(6)	117.34(11)
C(4)-C(1)-C(6)	102.32(11)	N(1)-C(1)-C(2)	101.00(10)
C(4)-C(1)-C(2)	111.96(11)	C(6)-C(1)-C(2)	112.01(11)
O(1)-C(2)-C(1)	103.97(10)	O(1)-C(2)-H(2A)	111.0
C(1)-C(2)-H(2A)	111.0	O(1)-C(2)-H(2B)	111.0
C(1)-C(2)-H(2B)	111.0	H(2A)-C(2)-H(2B)	109.0
O(1)-C(3)-N(1)	102.41(11)	O(1)-C(3)-C(15)	111.62(11)
N(1)-C(3)-C(15)	117.18(12)	O(1)-C(3)-H(3)	108.4
N(1)-C(3)-H(3)	108.4	C(15)-C(3)-H(3)	108.4
O(3)-C(4)-O(2)	122.01(13)	O(3)-C(4)-C(1)	128.03(12)
O(2)-C(4)-C(1)	109.92(11)	O(2)-C(5)-C(7)	109.47(12)
O(2)-C(5)-C(6)	105.44(10)	C(7)-C(5)-C(6)	115.14(12)
O(2)-C(5)-H(5)	108.9	C(7)-C(5)-H(5)	108.9
C(6)-C(5)-H(5)	108.9	O(4)-C(6)-C(5)	107.37(11)
O(4)-C(6)-C(1)	116.08(11)	C(5)-C(6)-C(1)	102.07(11)
O(4)-C(6)-H(6)	110.3	C(5)-C(6)-H(6)	110.3
C(1)-C(6)-H(6)	110.3	O(5)-C(7)-C(5)	107.62(11)
O(5)-C(7)-H(7A)	110.2	C(5)-C(7)-H(7A)	110.2
O(5)-C(7)-H(7B)	110.2	C(5)-C(7)-H(7B)	110.2
H(7A)-C(7)-H(7B)	108.5	O(6)-C(8)-O(5)	124.31(13)
O(6)-C(8)-C(9)	124.43(14)	O(5)-C(8)-C(9)	111.26(12)
C(14)-C(9)-C(10)	120.43(13)	C(14)-C(9)-C(8)	118.16(13)
C(10)-C(9)-C(8)	121.40(13)	C(11)-C(10)-C(9)	119.52(15)
C(11)-C(10)-H(10)	120.2	C(9)-C(10)-H(10)	120.2
C(12)-C(11)-C(10)	118.34(16)	C(12)-C(11)-H(11)	120.8
C(10)-C(11)-H(11)	120.8	C(13)-C(12)-C(11)	123.16(14)
C(13)-C(12)-N(2)	118.87(15)	C(11)-C(12)-N(2)	117.96(15)
C(12)-C(13)-C(14)	118.11(14)	C(12)-C(13)-H(13)	120.9
C(14)-C(13)-H(13)	120.9	C(9)-C(14)-C(13)	120.41(15)
C(9)-C(14)-H(14)	119.8	C(13)-C(14)-H(14)	119.8
C(17)-C(15)-C(18)	108.68(15)	C(17)-C(15)-C(16)	108.59(14)
C(18)-C(15)-C(16)	109.54(14)	C(17)-C(15)-C(3)	113.60(12)
C(18)-C(15)-C(3)	110.40(12)	C(16)-C(15)-C(3)	105.94(14)
C(15)-C(16)-H(16A)	109.5	C(15)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5	C(15)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5	H(16B)-C(16)-H(16C)	109.5
C(15)-C(17)-H(17A)	109.5	C(15)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5	C(15)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5	H(17B)-C(17)-H(17C)	109.5
C(15)-C(18)-H(18A)	109.5	C(15)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5	C(15)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5	H(18B)-C(18)-H(18C)	109.5
O(4)-C(19)-C(20)	112.92(13)	O(4)-C(19)-H(19A)	109.0
C(20)-C(19)-H(19A)	109.0	O(4)-C(19)-H(19B)	109.0
C(20)-C(19)-H(19B)	109.0	H(19A)-C(19)-H(19B)	107.8
C(25)-C(20)-C(21)	117.87(14)	C(25)-C(20)-C(19)	120.60(15)
C(21)-C(20)-C(19)	121.53(14)	C(22)-C(21)-C(20)	121.95(14)
C(22)-C(21)-H(21)	119.0	C(20)-C(21)-H(21)	119.0
C(21)-C(22)-C(23)	119.08(15)	C(21)-C(22)-H(22)	120.5
C(23)-C(22)-H(22)	120.5	O(7)-C(23)-C(24)	116.05(13)

O(7)-C(23)-C(22)	124.25(14)	C(24)-C(23)-C(22)	119.70(14)
C(23)-C(24)-C(25)	120.43(15)	C(23)-C(24)-H(24)	119.8
C(25)-C(24)-H(24)	119.8	C(20)-C(25)-C(24)	120.93(16)
C(20)-C(25)-H(25)	119.5	C(24)-C(25)-H(25)	119.5
O(7)-C(26)-H(26A)	109.5	O(7)-C(26)-H(26B)	109.5
H(26A)-C(26)-H(26B)	109.5	O(7)-C(26)-H(26C)	109.5
H(26A)-C(26)-H(26C)	109.5	H(26B)-C(26)-H(26C)	109.5
O(10)-C(27)-O(11)	126.35(11)	O(10)-C(27)-N(1)	121.91(12)
O(11)-C(27)-N(1)	111.74(11)	C(30A)-C(28)-O(11)	108.0(5)
C(30A)-C(28)-C(31)	130.1(5)	O(11)-C(28)-C(31)	111.0(2)
C(30A)-C(28)-C(29A)	119.9(7)	O(11)-C(28)-C(29A)	98.0(3)
C(31)-C(28)-C(29A)	84.1(5)	C(30A)-C(28)-C(29)	86.9(5)
O(11)-C(28)-C(29)	104.32(16)	C(31)-C(28)-C(29)	111.7(2)
C(29A)-C(28)-C(29)	33.6(4)	C(30A)-C(28)-C(30)	22.4(5)
O(11)-C(28)-C(30)	110.9(2)	C(31)-C(28)-C(30)	111.5(3)
C(29A)-C(28)-C(30)	137.8(5)	C(29)-C(28)-C(30)	107.1(2)
C(30A)-C(28)-C(31A)	114.1(7)	O(11)-C(28)-C(31A)	109.0(5)
C(31)-C(28)-C(31A)	22.3(4)	C(29A)-C(28)-C(31A)	106.4(6)
C(29)-C(28)-C(31A)	131.4(4)	C(30)-C(28)-C(31A)	92.9(5)
C(28)-C(29)-H(29A)	109.5	C(28)-C(29)-H(29B)	109.5
C(28)-C(29)-H(29C)	109.5	C(28)-C(30)-H(30A)	109.5
C(28)-C(30)-H(30B)	109.5	C(28)-C(30)-H(30C)	109.5
C(28)-C(31)-H(31A)	109.5	C(28)-C(31)-H(31B)	109.5
C(28)-C(31)-H(31C)	109.5	C(28)-C(29A)-H(29D)	109.5
C(28)-C(29A)-H(29E)	109.5	H(29D)-C(29A)-H(29E)	109.5
C(28)-C(29A)-H(29F)	109.5	H(29D)-C(29A)-H(29F)	109.5
H(29E)-C(29A)-H(29F)	109.5	C(28)-C(30A)-H(30D)	109.5
C(28)-C(30A)-H(30E)	109.5	H(30D)-C(30A)-H(30E)	109.5
C(28)-C(30A)-H(30F)	109.5	H(30D)-C(30A)-H(30F)	109.5
H(30E)-C(30A)-H(30F)	109.5	C(28)-C(31A)-H(31D)	109.5
C(28)-C(31A)-H(31E)	109.5	H(31D)-C(31A)-H(31E)	109.5
C(28)-C(31A)-H(31F)	109.5	H(31D)-C(31A)-H(31F)	109.5
H(31E)-C(31A)-H(31F)	109.5		

Symmetry transformations used to generate equivalent atoms:

**Table 4 - Anisotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for 280. The anisotropic displacement factor exponent takes the form:  $-2 \pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$**

Atom	U11	U22	U33	U23	U13	U12
O(1)	28(1)	43(1)	29(1)	-2(1)	-3(1)	2(1)
O(2)	38(1)	31(1)	26(1)	0(1)	10(1)	-3(1)
O(3)	37(1)	27(1)	31(1)	1(1)	6(1)	3(1)
O(4)	50(1)	30(1)	29(1)	2(1)	-9(1)	7(1)
O(5)	50(1)	37(1)	27(1)	6(1)	2(1)	-15(1)
O(6)	54(1)	37(1)	39(1)	5(1)	12(1)	-13(1)
O(7)	69(1)	46(1)	32(1)	-5(1)	2(1)	-13(1)
O(8)	83(1)	70(1)	35(1)	4(1)	2(1)	-3(1)
O(9)	63(1)	64(1)	55(1)	-13(1)	-16(1)	-5(1)
O(10)	29(1)	44(1)	23(1)	2(1)	1(1)	-7(1)
O(11)	32(1)	48(1)	21(1)	-10(1)	3(1)	0(1)
N(1)	26(1)	32(1)	21(1)	-2(1)	2(1)	-1(1)
N(2)	50(1)	53(1)	37(1)	-8(1)	-1(1)	3(1)
C(1)	30(1)	27(1)	20(1)	-1(1)	0(1)	0(1)
C(2)	32(1)	34(1)	24(1)	-2(1)	-1(1)	-2(1)
C(3)	25(1)	41(1)	27(1)	-5(1)	1(1)	1(1)
C(4)	31(1)	29(1)	17(1)	-3(1)	2(1)	-3(1)
C(5)	45(1)	30(1)	20(1)	3(1)	2(1)	-4(1)
C(6)	36(1)	25(1)	20(1)	1(1)	-4(1)	-1(1)
C(7)	53(1)	40(1)	24(1)	5(1)	5(1)	-13(1)
C(8)	34(1)	31(1)	34(1)	0(1)	9(1)	-6(1)
C(9)	31(1)	34(1)	33(1)	0(1)	7(1)	-3(1)
C(10)	47(1)	42(1)	35(1)	4(1)	0(1)	-14(1)
C(11)	54(1)	49(1)	35(1)	6(1)	3(1)	-11(1)
C(12)	37(1)	47(1)	31(1)	-5(1)	1(1)	-1(1)
C(13)	40(1)	37(1)	46(1)	-9(1)	4(1)	-6(1)
C(14)	41(1)	33(1)	42(1)	-2(1)	8(1)	-5(1)
C(15)	32(1)	47(1)	31(1)	-3(1)	3(1)	-10(1)
C(16)	34(1)	76(1)	61(1)	-10(1)	12(1)	-14(1)
C(17)	45(1)	37(1)	40(1)	-1(1)	6(1)	-11(1)
C(18)	70(1)	57(1)	33(1)	2(1)	5(1)	-26(1)
C(19)	39(1)	33(1)	49(1)	-3(1)	-6(1)	9(1)
C(20)	35(1)	26(1)	37(1)	1(1)	0(1)	9(1)
C(21)	62(1)	31(1)	27(1)	2(1)	7(1)	2(1)
C(22)	50(1)	26(1)	34(1)	1(1)	13(1)	-1(1)
C(23)	46(1)	30(1)	30(1)	-2(1)	5(1)	2(1)
C(24)	70(1)	48(1)	32(1)	-3(1)	19(1)	-9(1)
C(25)	47(1)	39(1)	45(1)	-1(1)	17(1)	-2(1)
C(26)	47(1)	38(1)	53(1)	-6(1)	2(1)	-3(1)
C(27)	30(1)	24(1)	21(1)	0(1)	2(1)	1(1)
C(28)	41(1)	47(1)	18(1)	-8(1)	2(1)	-2(1)
C(29)	50(2)	56(2)	25(1)	-4(1)	13(1)	-5(1)
C(30)	52(2)	37(2)	24(2)	6(1)	2(1)	3(1)
C(31)	65(2)	32(2)	25(2)	-8(1)	5(2)	-4(2)
C(29A)	61(4)	186(11)	27(3)	-22(5)	9(3)	20(6)
C(30A)	157(12)	44(4)	25(3)	10(3)	-7(7)	-5(6)
C(31A)	111(9)	78(6)	24(3)	-27(3)	4(5)	-20(7)

**Table 5 - Hydrogen coordinates (  $\times 10^4$ ) and isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for 280**

Atom	x	y	z	U(eq)
H(2A)	1293	1134	-28	37
H(2B)	1439	-298	299	37
H(3)	309	1044	2055	38
H(5)	3909	2068	-160	39
H(6)	4011	2649	1516	34
H(7A)	6518	2739	169	48
H(7B)	5389	3842	320	48
H(10)	7280	2329	2745	51
H(11)	8504	2303	4148	57
H(13)	10285	5761	3935	50
H(14)	9113	5766	2532	46
H(16A)	-1927	-1720	1703	85
H(16B)	-1895	-618	1058	85
H(16C)	-1900	-280	1984	85
H(17A)	1891	-1835	1411	62
H(17B)	275	-1762	758	62
H(17C)	512	-2738	1503	62
H(18A)	346	-2069	2859	81
H(18B)	492	-610	3102	81
H(18C)	1919	-1335	2894	81
H(19A)	1070	3178	1427	52
H(19B)	700	4318	788	52
H(21)	3583	5519	897	49
H(22)	5218	6831	1816	43
H(24)	3548	5374	3653	59
H(25)	2002	4006	2735	51
H(26A)	7150	7367	2917	71
H(26B)	6991	8321	3629	71
H(26C)	5835	8419	2747	71
H(29A)	1543	1283	4407	64
H(29B)	2944	942	5160	64
H(29C)	2228	-115	4502	64
H(30A)	4526	-652	4036	58
H(30B)	5343	116	4839	58
H(30C)	5739	432	3981	58
H(31A)	4852	2683	3874	62
H(31B)	4830	2489	4815	62
H(31C)	3349	3037	4185	62
H(29D)	1910	2384	4197	137
H(29E)	2724	1706	5037	137
H(29F)	1510	950	4353	137
H(30D)	3598	-713	4135	120
H(30E)	4752	-53	4892	120
H(30F)	5191	-146	4024	120
H(31D)	5584	2053	3870	110
H(31E)	5188	2467	4712	110
H(31F)	4204	3013	3863	110

Table 6 - Dihedral angles [°] for 280

Atom1 - Atom2 - Atom3 - Atom4	Dihedral
C(27) - N(1) - C(1) - C(4)	65.55(15)
C(3) - N(1) - C(1) - C(4)	-130.12(12)
C(27) - N(1) - C(1) - C(6)	-52.85(16)
C(3) - N(1) - C(1) - C(6)	111.48(13)
C(27) - N(1) - C(1) - C(2)	-174.87(11)
C(3) - N(1) - C(1) - C(2)	-10.55(14)
C(3) - O(1) - C(2) - C(1)	-37.24(14)
N(1) - C(1) - C(2) - O(1)	27.92(13)
C(4) - C(1) - C(2) - O(1)	147.96(11)
C(6) - C(1) - C(2) - O(1)	-97.76(13)
C(2) - O(1) - C(3) - N(1)	29.77(14)
C(2) - O(1) - C(3) - C(15)	-96.41(13)
C(27) - N(1) - C(3) - O(1)	151.82(13)
C(1) - N(1) - C(3) - O(1)	-10.58(14)
C(27) - N(1) - C(3) - C(15)	-85.69(17)
C(1) - N(1) - C(3) - C(15)	111.91(13)
C(5) - O(2) - C(4) - O(3)	177.91(12)
C(5) - O(2) - C(4) - C(1)	0.19(13)
N(1) - C(1) - C(4) - O(3)	36.41(18)
C(6) - C(1) - C(4) - O(3)	163.30(13)
C(2) - C(1) - C(4) - O(3)	-76.59(17)
N(1) - C(1) - C(4) - O(2)	-146.04(10)
C(6) - C(1) - C(4) - O(2)	-19.15(13)
C(2) - C(1) - C(4) - O(2)	100.96(12)
C(4) - O(2) - C(5) - C(7)	143.76(11)
C(4) - O(2) - C(5) - C(6)	19.35(13)
C(19) - O(4) - C(6) - C(5)	-158.16(12)
C(19) - O(4) - C(6) - C(1)	88.44(15)
O(2) - C(5) - C(6) - O(4)	-152.48(10)
C(7) - C(5) - C(6) - O(4)	86.74(14)
O(2) - C(5) - C(6) - C(1)	-29.93(12)
C(7) - C(5) - C(6) - C(1)	-150.71(12)
N(1) - C(1) - C(6) - O(4)	-90.80(14)
C(4) - C(1) - C(6) - O(4)	145.42(11)
C(2) - C(1) - C(6) - O(4)	25.35(16)
N(1) - C(1) - C(6) - C(5)	152.80(11)
C(4) - C(1) - C(6) - C(5)	29.02(12)
C(2) - C(1) - C(6) - C(5)	-91.05(13)
C(8) - O(5) - C(7) - C(5)	-157.68(13)
O(2) - C(5) - C(7) - O(5)	-65.14(15)
C(6) - C(5) - C(7) - O(5)	53.41(17)
C(7) - O(5) - C(8) - O(6)	-3.1(2)
C(7) - O(5) - C(8) - C(9)	177.43(13)
O(6) - C(8) - C(9) - C(14)	0.2(2)
O(5) - C(8) - C(9) - C(14)	179.67(14)
O(6) - C(8) - C(9) - C(10)	-179.26(16)
O(5) - C(8) - C(9) - C(10)	0.3(2)
C(14) - C(9) - C(10) - C(11)	-1.3(3)
C(8) - C(9) - C(10) - C(11)	178.08(16)

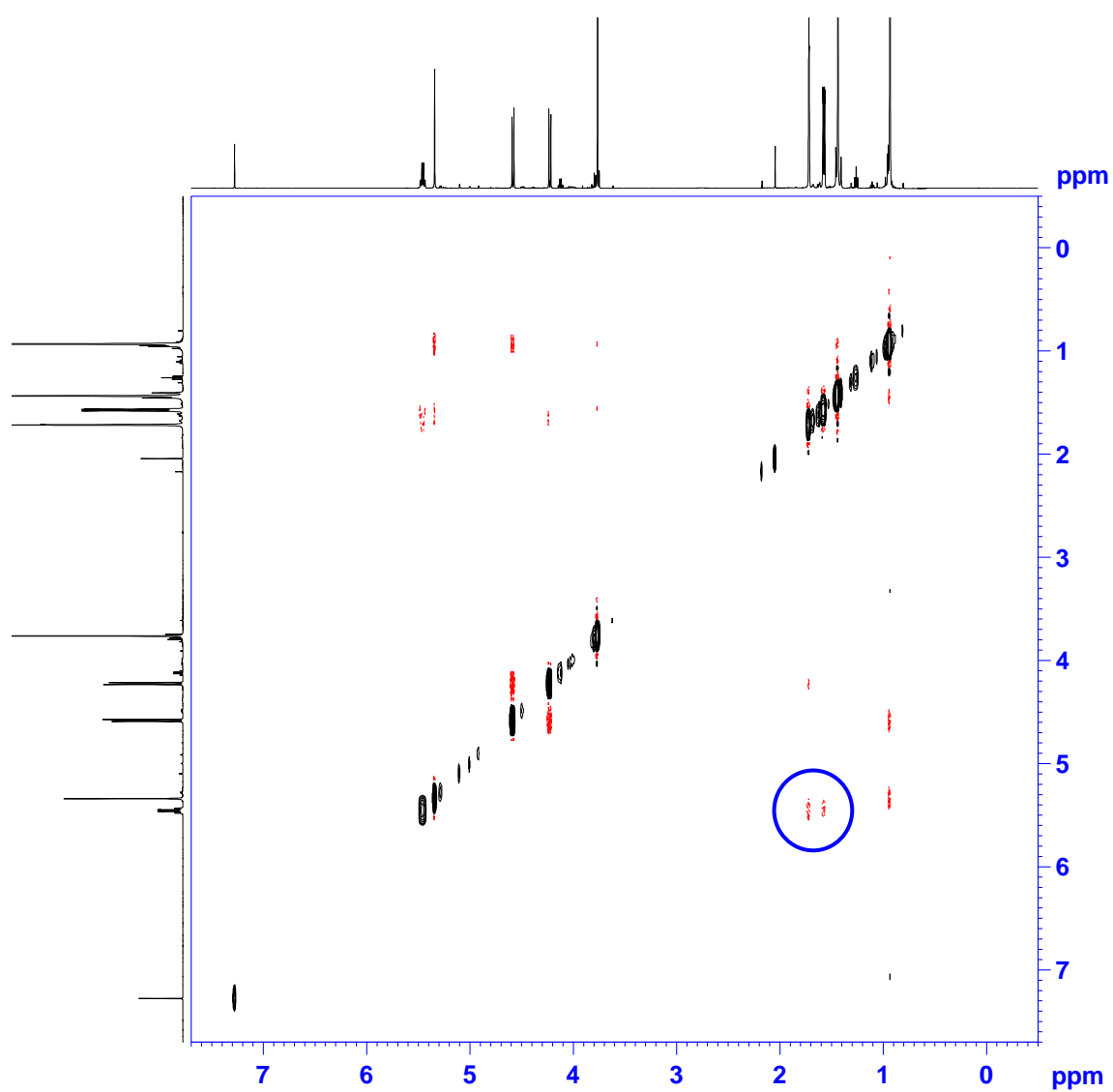
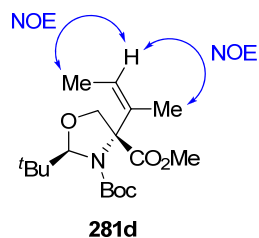
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C(9) - C(10) - C(11) - C(12)	0.8(3)
C(10) - C(11) - C(12) - C(13)	0.4(3)
C(10) - C(11) - C(12) - N(2)	-178.39(17)
O(9) - N(2) - C(12) - C(13)	-4.1(2)
O(8) - N(2) - C(12) - C(13)	176.08(16)
O(9) - N(2) - C(12) - C(11)	174.81(17)
O(8) - N(2) - C(12) - C(11)	-5.0(2)
C(11) - C(12) - C(13) - C(14)	-1.2(3)
N(2) - C(12) - C(13) - C(14)	177.58(15)
C(10) - C(9) - C(14) - C(13)	0.5(2)
C(8) - C(9) - C(14) - C(13)	-178.91(15)
C(12) - C(13) - C(14) - C(9)	0.7(2)
O(1) - C(3) - C(15) - C(17)	58.28(16)
N(1) - C(3) - C(15) - C(17)	-59.33(16)
O(1) - C(3) - C(15) - C(18)	-179.34(14)
N(1) - C(3) - C(15) - C(18)	63.05(18)
O(1) - C(3) - C(15) - C(16)	-60.83(16)
N(1) - C(3) - C(15) - C(16)	-178.44(13)
C(6) - O(4) - C(19) - C(20)	63.37(17)
O(4) - C(19) - C(20) - C(25)	-131.07(15)
O(4) - C(19) - C(20) - C(21)	49.79(19)
C(25) - C(20) - C(21) - C(22)	-0.4(2)
C(19) - C(20) - C(21) - C(22)	178.80(14)
C(20) - C(21) - C(22) - C(23)	-1.2(2)
C(26) - O(7) - C(23) - C(24)	178.90(15)
C(26) - O(7) - C(23) - C(22)	-1.4(2)
C(21) - C(22) - C(23) - O(7)	-178.52(15)
C(21) - C(22) - C(23) - C(24)	1.2(2)
O(7) - C(23) - C(24) - C(25)	-179.95(16)
C(22) - C(23) - C(24) - C(25)	0.3(3)
C(21) - C(20) - C(25) - C(24)	1.9(2)
C(19) - C(20) - C(25) - C(24)	-177.27(16)
C(23) - C(24) - C(25) - C(20)	-1.9(3)
C(28) - O(11) - C(27) - O(10)	-10.6(2)
C(28) - O(11) - C(27) - N(1)	170.06(12)
C(1) - N(1) - C(27) - O(10)	-17.35(19)
C(3) - N(1) - C(27) - O(10)	-178.74(13)
C(1) - N(1) - C(27) - O(11)	161.99(11)
C(3) - N(1) - C(27) - O(11)	0.60(19)
C(27) - O(11) - C(28) - C(30A)	-71.7(5)
C(27) - O(11) - C(28) - C(31)	76.6(2)
C(27) - O(11) - C(28) - C(29A)	163.3(5)
C(27) - O(11) - C(28) - C(29)	-163.03(17)
C(27) - O(11) - C(28) - C(30)	-48.0(2)
C(27) - O(11) - C(28) - C(31A)	52.9(5)

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## 8.2 2D-NOE Spectra

### 8.2.1 2D-NOE Spectra for 281d



## 9. REFERENCES

1. Ambrogelly, A.; Palioura, S.; Soll, D., *Nat. Chem. Biol.* **2007**, *3*, 29-35.
2. Rodnina, M. V.; Beringer, M.; Wintermeyer, W., *Trends. Biochem. Sci.* **2007**, *32*, 20-26.
3. Clayden, J.; Greeves, N.; Warren, S.; Wothers, P., *Organic Chemistry*. 6th ed.; Oxford University Press: 2001.
4. Furst, P.; Stehle, P., *J. Nutr.* **2004**, *134*, 1558S-1565S.
5. Young, V. R., *J. Nutr.* **1994**, *124*, 1517S-1523S.
6. Kimura, T.; Vassilev, V. P.; Shen, G.-J.; Wong, C.-H., *J. Am. Chem. Soc.* **1997**, *119*, 11734-11742.
7. Saeed, A.; Young, D. W., *Tetrahedron* **1992**, *48*, 2507-2514.
8. Miyata, O.; Asm, H.; Naito, T., *Chem. Pharm. Bull.* **2005**, *53*, 355-360.
9. Calne, R. Y.; Rolles, K.; Thiru, S.; McMaster, P.; Craddock, G. N.; Aziz, S.; White, D. J. G.; Evans, D. B.; Dunn, D. C.; Henderson, R. G.; Lewis, P., *The Lancet* **1979**, *314*, 1033-1036.
10. Wenger, R. M.; Martin, K.; Timbers, C.; Tromelin, A., *CHIMIA International Journal for Chemistry* **1992**, *46*, 314-322.
11. Campagne, J.-M., *Angew. Chem. Int. Ed.* **2007**, *46*, 8548-8552.
12. Guzman-Martinez, A.; Lamer, R.; Van Nieuwenhze, M. S., *J. Am. Chem. Soc.* **2007**, *129*, 6017-6021.
13. Osullivan, J.; McCullough, J. E.; Tymiak, A. A.; Kirsch, D. R.; Trejo, W. H.; Principe, P. A., *J. Antibiot.* **1988**, *41*, 1740-1744.
14. Maki, H.; Miura, K.; Yamano, Y., *Antimicrob. Agents Chemother.* **2001**, *45*, 1823-1827.
15. Caldwell, C. G.; Bondy, S. S., *Synthesis* **1990**, *1990*, 34-36.
16. Jung, M. E.; Jung, Y. H., *Tetrahedron Lett.* **1989**, *30*, 6637-6640.
17. Sunazuka, T.; Nagamitsu, T.; Tanaka, H.; Omura, S.; Sprengeler, P. A.; Smith, A. B., *Tetrahedron Lett.* **1993**, *34*, 4447-4448.
18. Cativiela, C.; D  a-de-Villegas, M. D.; G  lvez, J.; Garc  a, J., *Tetrahedron* **1996**, *52*, 9563-9574.
19. Fanning, K. N.; Jamieson, A. G.; Sutherland, A., *Org. Biomol. Chem.* **2005**, *3*, 3749-3756.
20. Gasparski, C. M.; Miller, M. J., *Tetrahedron* **1991**, *47*, 5367-5378.



21. Horikawa, M.; Busch-Petersen, J.; Corey, E. J., *Tetrahedron Lett.* **1999**, *40*, 3843-3846.
22. Thayumanavan, R.; Tanaka, F.; Barbas, C. F., *Org. Lett.* **2004**, *6*, 3541-3544.
23. MacMillan, J. B.; Molinski, T. F., *Org. Lett.* **2002**, *4*, 1883-1886.
24. Willis, M. C.; Cutting, G. A.; Piccio, V. J.-D.; Durbin, M. J.; John, M. P., *Angew. Chem.* **2005**, *117*, 1567-1569.
25. Jackson, B. G.; Pedersen, S. W.; Fisher, J. W.; Misner, J. W.; Gardner, J. P.; Staszak, M. A.; Doecke, C.; Rizzo, J.; Aikins, J.; Farkas, E.; Trinkle, K. L.; Vicenzi, J.; Reinhard, M.; Kroeff, E. P.; Higginbotham, C. A.; Gazak, R. J.; Zhang, T. Y., *Tetrahedron* **2000**, *56*, 5667-5677.
26. Carter, H. E.; Haines, W. J.; Ledyard, W. E.; Norris, W. P., *J. Biol. Chem.* **1947**, *169*, 77-82.
27. Merrill Jr., A. H., Chapter 13 - Sphingolipids. In *Biochemistry of Lipids, Lipoproteins and Membranes (Fifth Edition)*, Dennis, E. V.; Jean, E. V., Eds. Elsevier: San Diego, 2008; pp 363-397.
28. Thudichum, J. L. W., *A Treatise on the Chemical Constitution of Brain*. Bailliere, Tindall, and Cox: London, 1884.
29. Zheng, W.; Kollmeyer, J.; Symolon, H.; Momin, A.; Munter, E.; Wang, E.; Kelly, S.; Allegood, J. C.; Liu, Y.; Peng, Q.; Ramaraju, H.; Sullards, M. C.; Cabot, M.; Merrill Jr, A. H., *Biochim. Biophys. Acta* **2006**, *1758*, 1864-1884.
30. Hannun, Y. A.; Obeid, L. M., *J. Biol. Chem.* **2002**, *277*, 25847-25850.
31. Spiegel, S.; Milstien, S., *J. Biol. Chem.* **2002**, *277*, 25851-25854.
32. Hanada, K., *Jpn. J. Infect. Dis.* **2005**, *58*, 131-148.
33. Wang, E.; Norred, W. P.; Bacon, C. W.; Riley, R. T.; Merrill Jr, A. H., *J. Biol. Chem.* **1991**, *266*, 14486-14490.
34. Marasas, W. F. O.; Riley, R. T.; Hendricks, K. A.; Stevens, V. L.; Sadler, T. W.; Gelineau-Van Waes, J.; Missmer, S. A.; Cabrera, J.; Torres, O.; Gelderblom, W. C. A.; Allegood, J.; Martínez, C.; Maddox, J.; Miller, J. D.; Starr, L.; Sullards, M. C.; Roman, A. V.; Voss, K. A.; Wang, E.; Merrill Jr, A. H., *J. Nutr.* **2004**, *134*, 711-716.
35. Ogretmen, B.; Hannun, Y. A., *Nat. Rev. Cancer* **2004**, *4*, 604-616.
36. Schwartz, G. K.; Ward, D.; Saltz, L.; Casper, E. S.; Spiess, T.; Mullen, E.; Woodworth, J.; Venuti, R.; Zervos, P.; Storniolo, A. M.; Kelsen, D. P., *Clin. Cancer Res.* **1997**, *3*, 537-543.

37. Satoi, H.; Tomimoto, H.; Ohtani, R.; Kitano, T.; Kondo, T.; Watanabe, M.; Oka, N.; Akiguchi, I.; Furuya, S.; Hirabayashi, Y.; Okazaki, T., *Neuroscience* **2005**, *130*, 657-666.
38. Tamboli, I. Y.; Prager, K.; Barth, E.; Heneka, M.; Sandhoff, K.; Walter, J., *J. Biol. Chem.* **2005**, *280*, 28110-28117.
39. Han, X., *Curr. Alzheimer Res.* **2005**, *2*, 65-77.
40. Parekh, V. V.; Wilson, M. T.; Van Kaer, L., *Crit. Rev. Immunol.* **2005**, *25*, 183-213.
41. Kluepfel, D.; Bagli, J.; Baker, H.; Charest, M. P.; Kudelski, A., *J. Antibiot.* **1972**, *25*, 109-115.
42. Bagli, J.; Kluepfel, D.; St.-Jacques, M., *J. Org. Chem.* **1973**, *38*, 1253-1260.
43. Aragozzini, F.; Manachini, P. L.; Craveri, R.; Rindone, B.; Scolastico, C., *Tetrahedron* **1972**, *28*, 5493-5498.
44. Šašek, V.; Sailer, M.; Vokoun, J.; Musílek, V., *J. Basic Microbiol.* **1989**, *29*, 383-390.
45. Fujita, T.; Inoue, K.; Yamamoto, S.; Ikumoto, T.; Sasaki, S.; Toyama, R.; Chiba, K.; Hoshino, Y.; Okumoto, T., *J. Antibiot.* **1994**, *47*, 208-215.
46. Miyake, Y.; Kozutsumi, Y.; Nakamura, S.; Fujita, T.; Kawasaki, T., *Biochem. Biophys. Res. Commun.* **1995**, *211*, 396-403.
47. Du Toit, D. D.; Heydenrych, J. J.; Laker, L., *S. Afr. Med. J.* **1985**, *68*, 930-934.
48. NTP. *Report on Carcinogens, 12th Edition*; 2011; pp 125-126.
49. Sasaki, S.; Hashimoto, R.; Kiuchi, M.; Inoue, K.; Ikumoto, T.; Hirose, R.; Chiba, K.; Hoshino, Y.; Okumoto, T.; Fujita, T., *J. Antibiot.* **1994**, *47*, 420-433.
50. Fujita, T.; Hamamichi, N.; Kiuchi, M.; Matsuzaki, T.; Kitao, Y.; Inoue, K.; Hirose, R.; Yoneta, M.; Sasaki, S.; Chiba, K., *J. Antibiot.* **1996**, *49*, 846-853.
51. Fujita, T.; Inoue, K.; Yamamoto, S.; Ikumoto, T.; Sasaki, S.; Toyama, R.; Yoneta, M.; Chiba, K.; Hoshino, Y.; Okumoto, T., *J. Antibiot.* **1994**, *47*, 216-224.
52. Saab, G.; Almony, A.; Blinder, K. J.; Schuessler, R.; Brennan, D. C., *Arch. Ophthalmol.* **2008**, *126*, 140-141.
53. Westhoff, T. H.; Schmidt, S.; Glander, P.; Liefeld, L.; Martini, S.; Offermann, G.; Neumayer, H. H.; Zidek, W.; van der Giet, M.; Budde, K., *Nephrol. Dial. Transplant.* **2007**, *22*, 2354-2358.

54. Cohen, J. A.; Barkhof, F.; Comi, G.; Hartung, H.-P.; Khatri, B. O.; Montalban, X.; Pelletier, J.; Capra, R.; Gallo, P.; Izquierdo, G.; Tiel-Wilck, K.; de Vera, A.; Jin, J.; Stites, T.; Wu, S.; Aradhye, S.; Kappos, L., *N. Engl. J. Med.* **2010**, *362*, 402-415.
55. Novartis GILENYA Information. <http://www.gilenya.com/info/gilenya/what-is-gilenya.jsp?> (accessed 3rd February).
56. Huggins, A.; Sergott, R. C., *Curr. Opin. Ophthalmol.* **2011**, *22*, 447-450.
57. Kuo, C. H.; Wendler, N. L., *Tetrahedron Lett.* **1978**, *No. 3*, 211-214.
58. Just, G.; Payette, D. R., *Tetrahedron Lett.* **1980**, *21*, 3219-3222.
59. Payette, D. R.; Just, G., *Can. J. Chem.* **1981**, *59*, 269-282.
60. Banfi, L.; Beretta, M. G.; Colombo, L.; Gennari, C.; Scolastico, C., *J. Chem. Soc., Chem. Commun.* **1982**, 488-490.
61. Banfi, L.; Beretta, M. G.; Colombo, L.; Gennari, C.; Scolastico, C., *J. Chem. Soc., Perkin Trans. 1* **1983**, 1613-1619.
62. Inai, M.; Goto, T.; Furuta, T.; Wakimoto, T.; Kan, T., *Tetrahedron Asymmetry* **2008**, *19*, 2771-2773.
63. Yoshikawa, M.; Yokokawa, Y.; Okuno, Y.; Murakami, N., *Chem. Pharm. Bull.* **1994**, *42*, 994-996.
64. Yoshikawa, M.; Yokokawa, Y.; Okuno, Y.; Murakami, N., *Tetrahedron* **1995**, *51*, 6209-6228.
65. Sano, S.; Kobayashi, Y.; Kondo, T.; Takebayashi, M.; Maruyama, S.; Fujita, T.; Nagao, Y., *Tetrahedron Lett.* **1995**, *36*, 2097-2100.
66. Lee, K.-Y.; Oh, C.-Y.; Kim, Y.-H.; Joo, J.-E.; Ham, W.-H., *Tetrahedron Lett.* **2002**, *43*, 9361-9363.
67. Hatakeyama, S.; Yoshida, M.; Esumi, T.; Iwabuchi, Y.; Irle, H.; Kawamoto, T.; Yamada, H.; Nishizawa, M., *Tetrahedron Lett.* **1997**, *38*, 7887-7890.
68. Deloisy, S.; That Thang, T.; Olesker, A.; Lukacs, G., *Tetrahedron Lett.* **1994**, *35*, 4783-4786.
69. Rao, A. V. R.; Gurjar, M. K.; Devi, T. R.; Kumar, K. R., *Tetrahedron Lett.* **1993**, *34*, 1653-1656.
70. Jones, M. C.; Marsden, S. P., *Org. Lett.* **2008**, *10*, 4125-4128.
71. Sato, H.; Sato, K.; Iida, M.; Yamanaka, H.; Oishi, T.; Chida, N., *Tetrahedron Lett.* **2008**, *49*, 1943-1947.

72. Yamanaka, H.; Sato, K.; Sato, H.; Iida, M.; Oishi, T.; Chida, N., *Tetrahedron* **2009**, *65*, 9188-9201.
73. Oishi, T.; Ando, K.; Chida, N., *Chem. Commun.* **2001**, 1932-1933.
74. Chida, N.; Takeoka, J.; Tsutsumi, N.; Ogawa, S., *J. Chem. Soc., Chem. Commun.* **1995**, 793-794.
75. Chida, N.; Takeoka, J.; Ando, K.; Tsutsumi, N.; Ogawa, S., *Tetrahedron* **1997**, *53*, 16287-16298.
76. Oishi, T.; Ando, K.; Inomiya, K.; Sato, H.; Iida, M.; Chida, N., *Org. Lett.* **2001**, *4*, 151-154.
77. Shibata, K.; Shingu, K.; Vassiley, V. P.; Nishide, K.; Fujita, T.; Node, M.; Kajimoto, T.; Wong, C.-H., *Tetrahedron Lett.* **1996**, *37*, 2791-2794.
78. Nishide, K.; Shibata, K.; Fujita, T.; Kajimoto, T.; Wong, C.-H.; Node, M., *Heterocycles* **2000**, *52*, 1191-1201.
79. Fuiita, T.; Hamamichi, N.; Matsuzaki, T.; Kitao, Y.; Kiuchi, M.; Node, M.; Hiruse, R., *Tetrahedron Lett.* **1995**, *36*, 8599-8602.
80. Seebach, D.; Sting, A. R.; Hoffmann, M., *Angew. Chem. Int. Ed. Engl* **1996**, *35*, 2708-2748.
81. Iwabuchi, Y.; Furukawa, M.; Esumi, T.; Hatakeyama, S., *Chem. Commun.* **2001**, 2030-2031.
82. Berhal, F.; Takechi, S.; Kumagai, N.; Shibasaki, M., *Chem. Eur. J.* **2011**, *17*, 1915-1921.
83. Heathcock, C. H.; Streitwieser Jr., A., *Introduction to Organic Chemistry*. 2nd ed.; Macmillan Publishing Co., Inc.: 1981.
84. Lewis, E. S.; Boozer, C. E., *J. Am. Chem. Soc.* **1952**, *74*, 308-311.
85. Beagley, B.; Betts, M. J.; Pritchard, R. G.; Schofield, A.; Stoodley, R. J.; Vohra, S., *J. Chem. Soc., Chem. Commun.* **1991**, 924-925.
86. Seebach, D.; Wasmuth, D., *Angew. Chem. Int. Ed. Engl* **1981**, *20*, 971-971.
87. Seebach, D.; Naef, R., *Helv. Chim. Acta* **1981**, *64*, 2704-2708.
88. Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B., *J. Am. Chem. Soc.* **1983**, *105*, 5390-5398.
89. Seebach, D.; Aebi, J. D., *Tetrahedron Lett.* **1984**, *25*, 2545-2548.
90. Seebach, D.; Aebi, J. D.; Gander-Coquoz, M.; Naef, R., *Helv. Chim. Acta* **1987**, *70*, 1194-1216.

91. Seebach, D.; Amatsch, B.; Amstutz, R.; Beck, A. K.; Doler, M.; Egli, M.; Fitzi, R.; Gautschi, M.; Herradön, B.; Hidber, P. C.; Irwin, J. J.; Locher, R.; Maestro, M.; Maetzke, T.; Mouriño, A.; Pfammatter, E.; Plattner, D. A.; Schickli, C.; Schweizer, W. B.; Seiler, P.; Stucky, G.; Petter, W.; Escalante, J.; Juaristi, E.; Quintana, D.; Miravittles, C.; Molins, E., *Helv. Chim. Acta* **1992**, *75*, 913-934.
92. Naef, R.; Seebach, D., *Helv. Chim. Acta* **1985**, *68*, 135-143.
93. Seebach, D.; Naef, R.; Calderari, G., *Tetrahedron* **1984**, *40*, 1313-1324.
94. Naef, R.; Seebach, D., *Liebigs Ann. Chem.* **1983**, *1983*, 1930-1936.
95. Boeckman, R. K.; Yoon, S. K.; Heckendorn, D. K., *J. Am. Chem. Soc.* **1991**, *113*, 9682-9684.
96. Ogawa, T.; Niwa, H.; Yamada, K., *Tetrahedron* **1993**, *49*, 1571-1578.
97. Williams, R. M.; Glinka, T.; Kwast, E., *J. Am. Chem. Soc.* **1988**, *110*, 5927-5929.
98. Uno, H.; Baldwin, J. E.; Russell, A. T., *J. Am. Chem. Soc.* **1994**, *116*, 2139-2140.
99. Saijo, S.; Wada, M.; Himizu, J.; Ishida, A., *Chem. Pharm. Bull.* **1980**, *28*, 1449-58.
100. Thottathil, J. K.; Moniot, J. L.; Mueller, R. H.; Wong, M. K. Y.; Kissick, T. P., *J. Org. Chem.* **1986**, *51*, 3140-3143.
101. Pattenden, G.; Thom, S. M.; Jones, M. F., *Tetrahedron* **1993**, *49*, 2131-2138.
102. Mulqueen, G. C.; Pattenden, G.; Whiting, D. A., *Tetrahedron* **1993**, *49*, 5359-5364.
103. Jeanguenat, A.; Seebach, D., *J. Chem. Soc., Perkin Trans. I* **1991**, 2291-2298.
104. Pattenden, G.; Thom, S. M., *Synlett* **1992**, *1992*, 533,534.
105. Pattenden, G.; Thom, S. M., *J. Chem. Soc., Perkin Trans. I* **1993**, 1629-1636.
106. Boyce, R. J.; Pattenden, G., *Synlett* **1994**, *1994*, 587-588.
107. Boyce, R. J.; Mulqueen, G. C.; Pattenden, G., *Tetrahedron Lett.* **1994**, *35*, 5705-5708.
108. Corey, E. J.; Reichard, G. A., *J. Am. Chem. Soc.* **1992**, *114*, 10677-10678.
109. Stucky, G.; Seebach, D., *Chem. Ber.* **1989**, *122*, 2365-2375.
110. Roush, W. R.; Sciotti, R. J., *J. Am. Chem. Soc.* **1994**, *116*, 6457-6458.
111. Roush, W. R.; Sciotti, R. J., *Tetrahedron Lett.* **1992**, *33*, 4691-4694.
112. Roush, W. R.; Kageyama, M.; Riva, R.; Brown, B. B.; Warmus, J. S.; Moriarty, K. J., *J. Org. Chem.* **1991**, *56*, 1192-1210.

113. Fleming, I., *Pericyclic Reactions*. Oxford Science Publications: 2007.
114. Claisen, L., *Ber. Dtsch. Chem. Ges* **1912**, *45*, 3157-3166.
115. Cope, A. C.; Hardy, E. M., *J. Am. Chem. Soc.* **1940**, *62*, 441-444.
116. Hiersemann, M.; Nubbemeyer, U., *The Claisen Rearrangement*. Wiley-VCH: 2007.
117. Ziegler, F. E., *Chem. Rev.* **1988**, *88*, 1423-1452.
118. Vittorelli, P.; Winkler, T.; Hansen, H.-J.; Schmid, H., *Helv. Chim. Acta* **1968**, *51*, 1457-1461.
119. Hurd, C. D.; Pollack, M. A., *J. Am. Chem. Soc.* **1938**, *60*, 1905-1911.
120. Gajewski, J. J.; Conrad, N. D., *J. Am. Chem. Soc.* **1979**, *101*, 2747-2748.
121. Gajewski, J. J.; Conrad, N. D., *J. Am. Chem. Soc.* **1979**, *101*, 6693-6704.
122. Kinney, W. A.; Coghlan, M. J.; Paquette, L. A., *J. Am. Chem. Soc.* **1985**, *107*, 7352-7360.
123. Friedman, L.; Shechter, H., *J. Am. Chem. Soc.* **1961**, *83*, 3159-3160.
124. Sogo, S. G.; Widlanski, T. S.; Hoare, J. H.; Grimshaw, C. E.; Berchtold, G. A.; Knowles, J. R., *J. Am. Chem. Soc.* **1984**, *106*, 2701-2703.
125. Copley, S. D.; Knowles, J. R., *J. Am. Chem. Soc.* **1985**, *107*, 5306-5308.
126. March, J.; Smith, M. B., *March's Advanced Organic Chemistry*. 5th ed.; Wiley Interscience.
127. Vyvyan, J. R.; Oaksmith, J. M.; Parks, B. W.; Peterson, E. M., *Tetrahedron Lett.* **2005**, *46*, 2457-2460.
128. Macias, F. A.; Molinillo, J. M. G.; Varela, R. M.; Torres, A.; Fronczek, F. R., *J. Org. Chem.* **1994**, *59*, 8261-8266.
129. Meerwein, H.; Florian, W.; Schön, N.; Stopp, G., *Liebigs Ann.* **1961**, *641*, 1-39.
130. Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A., *Helv. Chim. Acta* **1964**, *47*, 2425-2429.
131. Felix, D.; Gschwend-Steen, K.; Wick, A. E.; Eschenmoser, A., *Helv. Chim. Acta* **1969**, *52*, 1030-1042.
132. Egert, E.; Beck, H.; Schmidt, D.; Gonschorrek, C.; Hoppe, D., *Tetrahedron Lett.* **1987**, *28*, 789-792.
133. Linton, E. C.; Kozlowski, M. C., *J. Am. Chem. Soc.* **2008**, *130*, 16162-16163.
134. Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-T.; Faulkner, D. J.; Petersen, M. R., *J. Am. Chem. Soc.* **1970**, *92*, 741-743.

135. Trost, B. M.; Pinkerton, A. B.; Seidel, M., *J. Am. Chem. Soc.* **2001**, *123*, 12466-12476.
136. Carroll, M. F., *J. Chem. Soc.* **1940**, 704-706.
137. Kimel, W.; Cope, A. C., *J. Am. Chem. Soc.* **1943**, *65*, 1992-1998.
138. Shimizu, I.; Yamada, T.; Tsuji, J., *Tetrahedron Lett.* **1980**, *21*, 3199-3202.
139. Burger, E. C.; Tunge, J. A., *Org. Lett.* **2004**, *6*, 4113-4115.
140. Overman, L. E., *J. Am. Chem. Soc.* **1974**, *96*, 597-599.
141. Nubbemeyer, U., *J. Org. Chem.* **1995**, *60*, 3773-3780.
142. Yu, C.-M.; Choi, H.-S.; Lee, J.; Jung, W.-H.; Kim, H.-J., *J. Chem. Soc., Perkin Trans. I* **1996**, 115-116.
143. Ireland, R. E.; Mueller, R. H., *J. Am. Chem. Soc.* **1972**, *94*, 5897-5898.
144. Tseou, H.-F.; Wang, Y.-T., *J. Chin. Chem. Soc.* **1937**, *5*, 224-229.
145. Chai, Y.; Hong, S.-p.; Lindsay, H. A.; McFarland, C.; McIntosh, M. C., *Tetrahedron* **2002**, *58*, 2905-2928.
146. Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S., *J. Am. Chem. Soc.* **1983**, *105*, 1988-2006.
147. Ireland, R. E.; Mueller, R. H.; Willard, A. K., *J. Org. Chem.* **1976**, *41*, 986-996.
148. Ireland, R. E.; Vevert, J. P., *J. Org. Chem.* **1980**, *45*, 4259-4260.
149. Ireland, R. E.; Wuts, P. G. M.; Ernst, B., *J. Am. Chem. Soc.* **1981**, *103*, 3205-3207.
150. Ireland, R. E.; Smith, M. G., *J. Am. Chem. Soc.* **1988**, *110*, 854-860.
151. Ireland, R. E.; Norbeck, D. W., *J. Am. Chem. Soc.* **1985**, *107*, 3279-3285.
152. Ireland, R. E.; Mueller, R. H.; Willard, A. K., *J. Am. Chem. Soc.* **1976**, *98*, 2868-2877.
153. Ireland, R. E.; Wipf, P.; Xiang, J. N., *J. Org. Chem.* **1991**, *56*, 3572-3582.
154. Ireland, R. E.; Willard, A. K., *Tetrahedron Lett.* **1975**, *16*, 3975-3978.
155. Bartlett, P. A.; Barstow, J. F., *J. Org. Chem.* **1982**, *47*, 3933-3941.
156. Matsui, S.; Oka, N.; Hashimoto, Y.; Saigo, K., *Enantiomer* **2000**, *5*, 105-108.
157. Morley, C.; Knight, D. W.; Share, A. C., *J. Chem. Soc., Perkin Trans. I* **1994**, 2903-2907.
158. Bartlett, P. A.; Tanzella, D. J.; Barstow, J. F., *Tetrahedron Lett.* **1982**, *23*, 619-622.
159. Kazmaier, U., *Leibigs Ann.* **1997**, *1997*, 285-295.
160. Kübel, B.; Höfle, G.; Steglich, W., *Angew. Chem. Int. Ed. Engl* **1975**, *14*, 58-59.

161. Kazmaier, U., *J. Org. Chem.* **1996**, *61*, 3694-3699.
162. Kazmaier, U.; Görbitz, C. H., *Synthesis* **1996**, 1489-1493.
163. Kazmaier, U.; Maier, S., *Tetrahedron* **1996**, *52*, 941-954.
164. Kazmaier, U.; Schneider, C., *Synlett* **1996**, *1996*, 975-977.
165. Quirin, C.; Kazmaier, U., *Synthesis* **2009**, 1725-1731.
166. Kazmaier, U., *Angew. Chem. Int. Ed. Engl* **1994**, *33*, 998-999.
167. Kazmaier, U.; Maier, S., *J. Chem. Soc., Chem. Commun.* **1995**, 1991-1992.
168. Kazmaier, U., *Synlett* **1995**, 1138-1140.
169. Kazmaier, U.; Krebs, A., *Tetrahedron Lett.* **1996**, *37*, 7945-7946.
170. Heimgartner, H., *Angew. Chem. Int. Ed. Engl* **1991**, *30*, 238-264.
171. Schipper, D., *J. Antibiot.* **1983**, *36*, 1076-1077.
172. Tellam, J. P.; Kociok-Köhn, G.; Carbery, D. R., *Org. Lett.* **2008**, *10*, 5199-5202.
173. Tellam, J. P.; Carbery, D. R., *J. Org. Chem.* **2010**, *75*, 7809-7821.
174. Tellam, J. P.; Carbery, D. R., *Tetrahedron Lett.* **2011**, *52*, 6027-6029.
175. Glorius, F.; Neuburger, M.; Pfaltz, A., *Helv. Chim. Acta* **2001**, *84*, 3178-3196.
176. Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S., *J. Org. Chem.* **1980**, *45*, 48-61.
177. Ireland, R. E.; Wilcox, C. S., *Tetrahedron Lett.* **1977**, *18*, 2839-2842.
178. Achmatowicz, M.; Szumna, A.; Zielinski, T.; Jurczak, J., *Tetrahedron* **2005**, *61*, 9031-9041.
179. Tellam, J. P. An Ireland-Claisen approach to beta-hydroxy alpha-amino acids. Thesis (Doctor of Philosophy (PhD)), University of Bath, 2010.
180. Collum, D. B.; Godenschwager, P. F., *J. Am. Chem. Soc.* **2008**, *130*, 8726-8732.
181. Harker, W. R. R. A mechanistic insight into the synthesis of enantiopure  $\beta$ -amino acids using the enamido Ireland Claisen rearrangement. Thesis (Doctor of Philosophy (PhD)), University of Bath, 2011.
182. Tellam, J. P., Unpublished PhD results. University of Bath: 2010.
183. Yu, S.; Pan, X.; Ma, D., *Chem. Eur. J.* **2006**, *12*, 6572-6584.
184. Falorni, M.; Conti, S.; Giacomelli, G.; Cossu, S.; Soccolini, F., *Tetrahedron: Asymmetry* **1995**, *6*, 287-294.
185. Kurth, M. J.; Decker, O. H. W.; Hope, H.; Yanuck, M. D., *J. Am. Chem. Soc.* **1985**, *107*, 443-448.
186. Gilbert, J. C.; Yin, J.; Fakhreddine, F. H.; Karpinski, M. L., *Tetrahedron* **2004**, *60*, 51-60.



187. Ishizaki, M.; Niimi, Y.; Hoshino, O., *Chem. Lett.* **2001**, 30, 546-547.
188. Kallmerten, J.; Gould, T. J., *J. Org. Chem.* **1986**, 51, 1152-1155.
189. Renaud, P.; Seebach, D., *Angew. Chem. Int. Ed. Engl* **1986**, 25, 843-844.
190. Seebach, D.; Stucky, G., *Angew. Chem. Int. Ed. Engl* **1988**, 27, 1351-1353.
191. Ghosez, L.; Yang, G.; Cagnon, J. R.; Bideau, F. L.; Marchand-Brynaert, J., *Tetrahedron* **2004**, 60, 7591-7606.
192. Brunner, M.; Koskinen, A. M. P., *Tetrahedron Lett.* **2004**, 45, 3063-3065.
193. Gharpure, S. J.; Shukla, M. K.; Vijayasree, U., *Org. Lett.* **2009**, 11, 5466-5469.
194. Kerrigan, N. J.; Upadhyay, T.; Procter, D. J., *Tetrahedron Lett.* **2004**, 45, 9087-9090.
195. Fan, M.-J.; Li, G.-Q.; Liang, Y.-M., *Tetrahedron* **2006**, 62, 6782-6791.
196. Brunner, M.; Saarenketo, P.; Straub, T.; Rissanen, K.; Koskinen, Ari M. P., *Eur. J. Org. Chem.* **2004**, 2004, 3879-3883.
197. Brunner, M.; Nissinen, M.; Rissanen, K.; Straub, T.; Koskinen, A. M. P., *J. Mol. Struct.* **2005**, 734, 177-182.
198. Di Giacomo, M.; Vinci, V.; Serra, M.; Colombo, L., *Tetrahedron: Asymmetry* **2008**, 19, 247-257.
199. Andrews, M. D.; Brewster, A.; Moloney, M. G., *Tetrahedron: Asymmetry* **1994**, 5, 1477-1478.
200. Zhang, J.; Flippen-Anderson, J. L.; Kozikowski, A. P., *J. Org. Chem.* **2001**, 66, 7555-7559.
201. Ling, T.; Macherla, V. R.; Manam, R. R.; McArthur, K. A.; Potts, B. C. M., *Org. Lett.* **2007**, 9, 2289-2292.
202. Ling, T.; Potts, B. C.; Macherla, V. R., *J. Org. Chem.* **2010**, 75, 3882-3885.
203. Katagiri, K.; Tori, K.; Kimura, Y.; Yoshida, T.; Nagasaki, T.; Minato, H., *J. Med. Chem.* **1967**, 10, 1149-1154.
204. Kohno, T.; Kohda, D.; Haruki, M.; Yokoyama, S.; Miyazawa, T., *J. Biol. Chem.* **1990**, 265, 6931-6935.
205. Kataoka, Y.; Matsumoto, O.; Tani, K., *Chem. Lett.* **1996**, 25, 727-728.
206. Krebs, O.; Taylor, R. J. K., *Org. Lett.* **2005**, 7, 1063-1066.
207. Work conducted in conjunction with Ryan Cavilla towards his MChem Research Project.
208. Curran, D. P.; Suh, Y. G., *J. Am. Chem. Soc.* **1984**, 106, 5002-5004.

209. Coates, R. M.; Rogers, B. D.; Hobbs, S. J.; Curran, D. P.; Peck, D. R., *J. Am. Chem. Soc.* **1987**, *109*, 1160-1170.
210. Cavilla, R. Synthesis of Stereospecific Quaternary Centres of  $\beta$ -Hydroxy- $\alpha$ -Amino Acids Utilising the Ireland-Claisen Rearrangement. MChem Project Report, University of Bath, Bath, 2010.
211. Riveiros, R.; Rodríguez, D.; Pérez Sestelo, J.; Sarandeses, L. A., *Org. Lett.* **2006**, *8*, 1403-1406.
212. Krause, N.; Hoffmann-Röder, A., Allenic Natural Products and Pharmaceuticals. In *Modern Allene Chemistry*, Wiley-VCH Verlag GmbH: 2008; pp 997-1040.
213. Ma, S., *Acc. Chem. Res.* **2009**, *42*, 1679-1688.
214. Dorange, I.; Löfstedt, J.; Närhi, K.; Franzén, J.; Bäckvall, J.-E., *Chem. Eur. J.* **2003**, *9*, 3445-3449.
215. Ma, S., Ionic Additions to Allenes. In *Modern Allene Chemistry*, Wiley-VCH Verlag GmbH: 2008; pp 595-699.
216. Murakami, M.; Matsuda, T., Cycloadditions of Allenes. In *Modern Allene Chemistry*, Wiley-VCH Verlag GmbH: 2008; pp 727-815.
217. Palomo, C.; Aizpurua, J. M.; Balentová, E.; Azcune, I.; Santos, J. I.; Jiménez-Barbero, J. s.; Cañada, J.; Miranda, J. I., *Org. Lett.* **2008**, *10*, 2227-2230.
218. Nicolaou, K. C.; Bulger, P. G.; Sarlah, D., *Angew. Chem. Int. Ed.* **2005**, *44*, 4490-4527.
219. Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H., *Angew. Chem. Int. Ed. Engl* **1995**, *34*, 2039-2041.
220. Schwab, P.; Grubbs, R. H.; Ziller, J. W., *J. Am. Chem. Soc.* **1996**, *118*, 100-110.
221. Boivin, T. L. B., *Tetrahedron* **1987**, *43*, 3309-3362.
222. Koert, U.; Stein, M.; Wagner, H., *Chem. Eur. J.* **1997**, *3*, 1170-1180.
223. Franck, B.; Gehrken, H.-P., *Angew. Chem. Int. Ed. Engl* **1980**, *19*, 461-462.
224. Ganguli, M.; Burka, L. T.; Harris, T. M., *J. Org. Chem.* **1984**, *49*, 3762-3766.
225. Aksin, Ö.; Krause, N., *Adv. Synth. Catal.* **2008**, *350*, 1106-1112.
226. Diver, S. T.; Giessert, A. J., *Chem. Rev.* **2004**, *104*, 1317-1382.
227. Mori, M.; Sakakibara, N.; Kinoshita, A., *J. Org. Chem.* **1998**, *63*, 6082-6083.
228. Smulik, J. A.; Diver, S. T., *Org. Lett.* **2000**, *2*, 2271-2274.
229. Cagniant, P.; Cagniant, D., Recent Advances in the Chemistry of Benzo[b]furan and Its Derivatives. Part I: Occurrence and Synthesis. In *Adv. Heterocycl.*

- Chem.*, Katritzky, A. R.; Boulton, A. J., Eds. Academic Press: 1975; Vol. Volume 18, pp 337-482.
230. Zhou, L.; Shi, Y.; Xiao, Q.; Liu, Y.; Ye, F.; Zhang, Y.; Wang, J., *Org. Lett.* **2011**, *13*, 968-971.
231. Katritzky, A. R., *Comprehensive Heterocyclic Chemistry III*. 2008.
232. Liao, W.-W.; Ibrahim, I.; Cordova, A., *Chem. Commun.* **2006**, 674-676.
233. Kuroda, Y.; Okuhara, M.; Goto, T., *J. Antibiot.* **1980**, *33*, 132-136.
234. Chalet, L.; Arison, B. H.; Monaghan, R. L., *J. Antibiot.* **1984**, *37*, 207-210.
235. Rando, R. R., *Nature* **1974**, *250*, 586-587.
236. Bicknell, A. J.; Burton, G.; Elder, J. S., *Tetrahedron Lett.* **1988**, *29*, 3361-3364.
237. Armstrong, A.; Challinor, L.; Moir, J. H., *Angew. Chem. Int. Ed.* **2007**, *46*, 5369-5372.
238. Parsons, P. J.; Pennicott, L.; Eshelby, J.; Goessman, M.; Highton, A.; Hitchcock, P., *J. Org. Chem.* **2007**, *72*, 9387-9390.
239. Scheiper, B.; Bonnekesel, M.; Krause, H.; Furstner, A., *J. Org. Chem.* **2004**, *69*, 3943-3949.
240. Stewart, I. C.; Douglas, C. J.; Grubbs, R. H., *Org. Lett.* **2008**, *10*, 441-444.
241. Courchay, F. C.; Baughman, T. W.; Wagener, K. B., *J. Organomet. Chem.* **2006**, *691*, 585-594.
242. Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelter, R. A.; Bussmann, D. A.; Grubbs, R. H., *J. Am. Chem. Soc.* **1999**, *122*, 58-71.
243. Patani, G. A.; LaVoie, E. J., *Chem. Rev.* **1996**, *96*, 3147-3176.
244. Jerphagnon, T.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L., *Chem. Soc. Rev.* **2009**, *38*, 1039-1075.
245. Johnson, J. B.; Rovis, T., *Angew. Chem. Int. Ed.* **2008**, *47*, 840-871.
246. Sakai, M.; Hayashi, H.; Miyaura, N., *Organometallics* **1997**, *16*, 4229-4231.
247. Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N., *J. Am. Chem. Soc.* **1998**, *120*, 5579-5580.
248. Edwards, H. J.; Hargrave, J. D.; Penrose, S. D.; Frost, C. G., *Chem. Soc. Rev.* **2010**, *39*, 2093-2105.
249. Sakuma, S.; Miyaura, N., *J. Org. Chem.* **2001**, *66*, 8944-8946.
250. Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M., *J. Am. Chem. Soc.* **2002**, *124*, 5052-5058.

251. Hargrave, J. D.; Allen, J. C.; Frost, C. G., *Chemistry – An Asian Journal* **2010**, *5*, 386-396.
252. Okamoto, K.; Hayashi, T.; Rawal, V. H., *Org. Lett.* **2008**, *10*, 4387-4389.
253. Abel, E. W.; Stone, F. G. A.; Wilkinson, G., *Comprehensive Organometallic Chemistry II*. Pergamon: Oxford, 1995; Vol. 1-14.
254. Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K., *J. Am. Chem. Soc.* **2003**, *125*, 11508-11509.
255. Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M., *J. Am. Chem. Soc.* **2004**, *126*, 1628-1629.
256. Defieber, C.; Paquin, J.-F.; Serna, S.; Carreira, E. M., *Org. Lett.* **2004**, *6*, 3873-3876.
257. Trost, B. M.; Burns, A. C.; Tautz, T., *Org. Lett.* **2011**, *13*, 4566-4569.
258. Hu, X.; Zhuang, M.; Cao, Z.; Du, H., *Org. Lett.* **2009**, *11*, 4744-4747.
259. Wang, Y.; Hu, X.; Du, H., *Org. Lett.* **2010**, *12*, 5482-5485.
260. Maire, P.; Deblon, S.; Breher, F.; Geier, J.; Böhler, C.; Rüegger, H.; Schönberg, H.; Grützmacher, H., *Chem. Eur. J.* **2004**, *10*, 4198-4205.
261. Cao, Z.; Liu, Y.; Liu, Z.; Feng, X.; Zhuang, M.; Du, H., *Org. Lett.* **2011**, *13*, 2164-2167.
262. Shintani, R.; Narui, R.; Tsutsumi, Y.; Hayashi, S.; Hayashi, T., *Chem. Commun.* **2011**, *47*, 6123-6125.
263. Hahn, B. T.; Tewes, F.; Fröhlich, R.; Glorius, F., *Angew. Chem. Int. Ed.* **2010**, *49*, 1143-1146.
264. Jin, S.-S.; Wang, H.; Zhu, T.-S.; Xu, M.-H., *Org. Biomol. Chem.* **2012**, *10*, 1764-1768.
265. Thaler, T.; Guo, L.-N.; Steib, A. K.; Raducan, M.; Karaghiosoff, K.; Mayer, P.; Knochel, P., *Org. Lett.* **2011**, *13*, 3182-3185.
266. Qi, W.-Y.; Zhu, T.-S.; Xu, M.-H., *Org. Lett.* **2011**, *13*, 3410-3413.
267. Jin, S.-S.; Wang, H.; Xu, M.-H., *Chem. Commun.* **2011**, *47*, 7230-7232.
268. Feng, X.; Wang, Y.; Wei, B.; Yang, J.; Du, H., *Org. Lett.* **2011**, *13*, 3300-3303.
269. Feng, X.; Wei, B.; Yang, J.; Du, H., *Org. Biomol. Chem.* **2011**, *9*, 5927-5929.
270. Li, Q.; Dong, Z.; Yu, Z.-X., *Org. Lett.* **2011**, *13*, 1122-1125.
271. Baughman, T. W.; Sworen, J. C.; Wagener, K. B., *Tetrahedron* **2004**, *60*, 10943-10948.
272. Morikawa, S.; Michigami, K.; Amii, H., *Org. Lett.* **2010**, *12*, 2520-2523.

273. Liao, Y.-X.; Xing, C.-H.; Hu, Q.-S., *Org. Lett.* **2012**, *14*, 1544-1547.
274. Losse, G.; Müller, G., *Chem. Ber.* **1961**, *94*, 2768-2778.
275. Billman, J. H.; Harting, W. F., *J. Am. Chem. Soc.* **1948**, *70*, 1473-1474.
276. Shendage, D. M.; Frohlich, R.; Haufe, G., *Org. Lett.* **2004**, *6*, 3675-3678.
277. Calmes, M.; Daunis, J.; Mai, N., *Tetrahedron: Asymmetry* **1997**, *8*, 1641-1648.
278. Schoenenberger, H.; Endres, W., *Pharmazie* **1976**, *31*, 811-813.
279. Fling, M.; Minard, F. N.; Fox, S. W., *J. Am. Chem. Soc.* **1947**, *69*, 2466-2467.
280. Anderson, G. W.; McGregor, A. C., *J. Am. Chem. Soc.* **1957**, *79*, 6180-6183.
281. Meyers, A. I.; Tavares, F. X., *J. Org. Chem.* **1996**, *61*, 8207-8215.
282. Slotin, L. A.; Lauren, D. R.; Williams, R. E., *Can. J. Chem.* **1977**, *55*, 4257-4266.
283. Campbell, C. D.; Concellón, C.; Smith, A. D., *Tetrahedron: Asymmetry* **2011**, *22*, 797-811.
284. Baumgarten, H. E.; Dirks, J. E.; Petersen, J. M.; Zey, R. L., *J. Org. Chem.* **1966**, *31*, 3708-3711.
285. Ouchi, H.; Saito, Y.; Yamamoto, Y.; Takahata, H., *Org. Lett.* **2002**, *4*, 585-587.
286. Lan, H.-Q.; Ye, J.-L.; Wang, A.-E.; Ruan, Y.-P.; Huang, P.-Q., *Chem. Eur. J.* **2011**, *17*, 958-968.
287. Malkov, A. V.; Figlus, M.; Stončius, S.; Kočovský, P., *J. Org. Chem.* **2007**, *72*, 1315-1325.
288. Kitchin, J.; Bethell, R. C.; Cammack, N.; Dolan, S.; Evans, D. N.; Holman, S.; Holmes, D. S.; McMeekin, P.; Mo, C. L., *J. Med. Chem.* **1994**, *37*, 3707-3716.
289. Braibante, M. E. F.; Braibante, H. S.; Costenaro, E. R., *Synthesis* **1999**, *1999*, 943-946.
290. King, F. E.; Clark-Lewis, J. W.; Smith, G. R., *J. Chem. Soc.* **1954**, 1046-1049.
291. Cao, Y.; Christopherson, R.; Elix, J.; Gaul, K., *Aust. J. Chem.* **1994**, *47*, 903-911.
292. Falorni, M.; Satta, M.; Conti, S.; Giacomelli, G., *Tetrahedron: Asymmetry* **1993**, *4*, 2389-2398.
293. Groselj, U.; Bevk, D.; Jakse, R.; Meden, A.; Pirc, S.; Recnik, S.; Stanovnik, B.; Svete, J., *Tetrahedron: Asymmetry* **2004**, *15*, 2367-2383.
294. Kim, Y.-A.; Chung, H.-M.; Park, J.-S.; Choi, W.; Min, J.; Park, N.-H.; Kim, K.-H.; Jhon, G.-J.; Han, S.-Y., *J. Org. Chem.* **2003**, *68*, 10162-10165.
295. Sorrells, J. L.; Menger, F. M., *J. Am. Chem. Soc.* **2008**, *130*, 10072-10073.

296. Andrews, M. D.; Brewster, A. G.; Crapnell, K. M.; Ibbett, A. J.; Jones, T.; Moloney, M. G.; Prout, K.; Watkin, D., *J. Chem. Soc., Perkin Trans. 1* **1998**, 223-236.
297. Murata, T.; Mizobe, Y.; Gao, H.; Ishii, Y.; Wakabayashi, T.; Nakano, F.; Tanase, T.; Yano, S.; Hidai, M., *J. Am. Chem. Soc.* **1994**, *116*, 3389-3398.
298. Davies, A. G.; Hawari, J. A. A.; Muggleton, B.; Tse, M.-W., *J. Chem. Soc., Perkin Trans. 2* **1981**, 1132-1137.
299. Paterson, I.; Di Francesco, M. E.; Kühn, T., *Org. Lett.* **2003**, *5*, 599-602.
300. Möller, R.; Engel, N.; Steglich, W., *Synthesis* **1978**, 620.
301. Chen, G.; Gui, J.; Li, L.; Liao, J., *Angew. Chem. Int. Ed.* **2011**, *50*, 7681-7685.